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SCIENCE MEDICINES HEALTH

19 September 2019
EMA/547569/2019
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/II/0017

Marketing authorisation holder (MAH): sanofi-aventis groupe

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AERD	aspirin-exacerbated respiratory disease
AESI	adverse event of special interest
ANA	anti-nuclear antibody
ANCOVA	analysis of covariance
BID	twice daily
CDF	cumulative distribution function
CMQ	custom MedDRA queries
CPK	creatine phosphokinase
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis phenotype with nasal polyps
CYP	cytochrome P
DBP	diastolic blood pressure
e-CRF	electronic case report form
ECP	eosinophilic cationic protein
EGPA	eosinophilic granulomatosis with polyangiitis
EOS	end of study
EOT	end of treatment
EQ-5D	European quality of life 5 dimension scale
FESS	functional endoscopy sinus surgery
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	Good Clinical Practice
HLGT	high-level group term
HLT	high-level term
HR	heart rate
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IMP	investigational medicinal product
ITT	intent to treat
LLOQ	lower limit of quantitation
LLT	lower-level term
LMK	Lund-Mackay
LTE4	leukotriene E4
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	mometasone furoate nasal spray
MI	multiple imputation
MMRM	mixed-effect model with repeated measures
MRI	magnetic resonance imaging
NC	nasal congestion
NPIF	nasal peak inspiratory flow
NPS	nasal polyps score
NSAID-ERD	non-steroidal anti-inflammatory drug exacerbated respiratory disease
OC	osteomeatal complex
OCS	oral corticosteroids
PCSA	potentially clinically significant abnormal result
PGDM	metabolite of prostaglandin D2

POC	proof of concept
PROs	patient reported outcomes
PT	preferred term
q2w	every 2 weeks
QD	once daily
QoL	quality of life
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SCS	systemic corticosteroids
SD	standard deviation
SEM	standard error of the mean
SMQ	standardized MedDRA queries
SNOT-22	22-item sino-nasal outcome test
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation-regulated chemokine
TEAE	treatment-emergent adverse event
TSS	total symptom score
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
VAS	visual analogue scale
WBC	white blood cells
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential
WOCF	worst observation carried forward

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 12 March 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication in adults patients with Chronic rhinosinusitis with nasal polyposis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
An updated RMP is submitted (V 4.0)

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0311/2015) issued on 21 December 2015 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did seek Scientific Advice at the CHMP in 2016 (EMA/H/SA/2744/2016/II).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	12 March 2019
Start of procedure:	30 March 2019
CHMP Co-Rapporteur Assessment Report	23 May 2019
CHMP Rapporteur Assessment Report	23 May 2019
PRAC Rapporteur Assessment Report	29 May 2019
Updated PRAC Rapporteur Assessment Report	6 June 2019
PRAC Outcome	13 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2019
Request for supplementary information (RSI)	27 June 2019
CHMP Rapporteur Assessment Report	20 August 2019
PRAC Rapporteur Assessment Report	21 August 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	4 September 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur Assessment Report	12 September 2019
Opinion	19 September 2019

2. Scientific discussion

2.1. Introduction

The current application seeks approval of dupilumab in severe chronic rhinosinusitis with nasal polyposis (CRSwNP). The proposed dose regimen is 300 mg q2w for dupilumab as an add-on treatment in adult patients with severe CRSwNP who are inadequately controlled with intranasal corticosteroids.

The proposed indication is as follows :

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on maintenance treatment in adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) who previously failed or are intolerant or contraindicated to systemic corticosteroids and/or surgery.

Dupixent is indicated to reduce the need for surgery and systemic corticosteroid use in adult patients with inadequately controlled severe CRSwNP.

2.2. Non-clinical aspects

2.2.1. Introduction

Non clinical safety was assessed as part of the original MAA for atopic dermatitis (AD) indication and no new pre-clinical toxicology studies are included in this submission. However, an updated amended carcinogenicity risk assessment is provided in this application.

2.2.2. Toxicology

Carcinogenicity

The document Amended Carcinogenicity Risk Assessment is an amended risk assessment to those previously submitted to Health Authorities. The purpose of this amendment was to reflect an updated literature search cut-off date in support of the marketing authorisation applicationfor the patients with chronic rhinosinusitis with nasal polyposis..

A literature search for any articles published between June 1, 2018 and January 31, 2019 was performed, and no new publications were identified that would change the conclusions of the original document. No changes have been made to the original document.

The conclusion stated in the original application remains the same.

In summary, the weight-of-evidence for the available literature data related to IL-4Rα inhibition, and animal toxicology data with surrogate antibodies REGN1103 and REGN646, do not support an increased risk of cancer for dupilumab. Hence, the MAH maintains that no additional nonclinical studies are necessary to evaluate the carcinogenic potential of dupilumab.

2.2.3. Ecotoxicity/environmental risk assessment

There was no update of the environmental risk assessment. It is considered that with this new indication the risk associated with environmental assessment would remain unchanged.

2.2.4. Discussion on non-clinical aspects

The updated information provided do not change previous conclusion made on carcinogenicity. There is no need to update the SmPC.

2.2.5. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of duplilumab.

The available non clinical data support the use of duplilumab in the proposed indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

Study number Study report location	Test article	Analytical method	Testing facility
	Population PK Study Reports		
[POH0668] Module 5.3.3.5	Functional dupilumab	population PK analysis _global base model	Sanofi US, Inc. Bridgewater, NJ, USA
[POH0611] Module 5.3.3.5	Functional dupilumab	population PK analysis _NP submission model	Sanofi US, Inc. Bridgewater, NJ, USA
[POH0687] Module 5.3.3.5	Functional dupilumab	empirical PKPD analysis in patients with NP for key efficacy endpoints_NP submission model	Sanofi US, Inc. Bridgewater, NJ, USA

PK: pharmacokinetics, NP: nasal polyposis, PD: pharmacodynamics

Type of study	**- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers**	**- Objective(s) of study - Study design and type of control**	**Test product(s): - Formulation - Dosage regimen - Route of administration**	**Reference therapy: - Formulation - Dosage regimen - Route of administration**	**ber of subjects - Total[a, b, c] - Gender[a] (M/F) - Race[a] (C/B/A/O) - Age[a] mean ± SD (range) - Treatment group[b]**	**Healthy subjects or diagnosis of patients**	**Duration of treatment**	**Study status Type of report**
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication – Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)								
Efficacy	- [ACT12340] - Module 5.3.5.1 in original marketing application for atopic dermatitis - Claus Bachert (University Hospital Ghent, Belgium)	- Efficacy, safety, PD and PK - A randomized, double-blind, phase 2, placebo controlled study	- Dupilumab was provided as a 150 mg/mL solution in 5 mL glass vials to deliver 300 mg in 2 mL - Dupilumab 600 mg on Day 1 + 300 mg qw - SC	- Matching placebo was provided in 5mL glass vials to deliver 2 mL - Placebo matched to dupilumab 600 mg on Day 1 + placebo matched to dupilumab 300 mg qw - SC	- 60/60/51 - 34/26 - 59/1/0/0 - 48.4 ± 9.4 (25-64) - 300 mg qw group: 30 / Placebo group: 30	Patients l NP and ıptoms of least 2 nasal nasal acial re;	16 weeks	Complete Full

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	ɔer of subjects - Total[a, b, c] - Gender[a] (M/F) - Race[a] (C/B/A/O) - Age[a] mean ± SD (range) - Treatment group[b]	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
	- 14 active centers in 4 countries		On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)	On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)		ss of		
Efficacy	- [EFC14146] SINUS-24 - Module 5.3.5.1 - Joseph Han MD (Eastern Virginia Medical School, United States) - 67 active centers in 13 countries	- Efficacy, safety and PK -A randomized, double-blind, placebo controlled study	- Dupilumab was provided as a 150 mg/mL solution in a glass prefilled syringe to deliver 300 mg in 2 mL. - Dupilumab 300 mg q2w - SC On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)	- Placebo for dupilumab was provided in an identically matched glass prefilled syringe to deliver 2 mL - Placebo matched to dupilumab 300 mg q2w - SC On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)	- 276/275/263 - 158/118 - 264/9/1/2 - 50.49 ± 13.39 (22-85) - 300 mg q2w group: 143 / Placebo group: 132	Patients with bilateral NP and chronic symptoms of sinusitis (nasal congestion and another symptom)	24 weeks	Complete Full
Efficacy	- [EFC14280] SINUS-52 - Module 5.3.5.1 - Claus Bachert MD (University Hospital Ghent, Belgium) - 117 active centers in 14 countries	- Efficacy, safety and PK - A randomized, double-blind, , placebo controlled study	- Dupilumab was provided as a 150 mg/mL solution in a glass prefilled syringe to deliver 300 mg in 2 mL. - Dupilumab 300 mg q2w until Week 52 / dupilumab 300 mg q2w until Week 24 then 300 mg q4w until Week 52 -SC On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)	- Placebo for dupilumab was provided in an identically matched glass prefilled syringes to deliver 2 mL. - Placebo matching dupilumab SC q2w administration until Week 52 - SC On a background therapy with MFNS 2 actuations (50 µg/actuation) in each nostril BID (total daily dose of 400 µg)	- 448/447/398 - 279/169 - 372/7/54/15 - 51.95 ± 12.45 (18-83) - 300 mg q2w-q4w group: 148 / 300 mg q2w group: 149 / Placebo group: 150	Patients with bilateral NP and chronic symptoms of sinusitis (nasal congestion and another symptom)	52 weeks	Complete Full (Primary anasysis completed)

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	ɔer of subjects - Total[a, b, c] - Gender[a] (M/F) - Race[a] (C/B/A/O) - Age[a] mean ± SD (range) - Treatment group[b]	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report

a Randomized.
b Treated.
c Completed study drug according to Investigator (end-of-treatment form).
M: male, F: female, C: Caucasian, B: black, A: Asian, O: other, SD: standard deviation, NA: not applicable, PK: pharmacokinetics: PD: pharmacodynamics, SC: subcutaneous, mL: milliliter, qw: every week, q2w: once every 2 weeks, q4w: once every 4 weeks, BID: twice daily, CRSwNP: chronic rhinosinusitis with nasal polyposis, NP: nasal polyposis, MFNS: mometasone furoate nasal spray, ACQ-6: Asthma Control Questionnaire, 6-question version, SNOT-22: 22-item sino-nasal outcome test, VAS: visual analog scale.

The PK profile of dupilumab was characterized in 6 Phase 1 studies conducted in adult healthy subjects (including Japanese subjects). The PK results from these Phase 1 clinical pharmacology studies in healthy subjects were previously presented in the original dupilumab marketing application in support of the adult AD indication.

The PK and PD profiles of dupilumab were assessed in adult patients with CRSwNP who were inadequately controlled with INCS in the Phase 2a study ACT12340 and in patients who had failed prior treatment with systemic corticosteroids and/or surgery in 2 pivotal Phase 3 studies (EFC14146 and EFC14280) for treatment periods ranging from 16 weeks to 52 weeks. A subcutaneous (SC) dosing regimen of 300 mg once every week (qw), following a loading dose of 600 mg on Day 1, was assessed in this Phase 2a study. Subsequently, the 300 mg once every 2 weeks (q2w) regimen without a loading dose was evaluated in Studies EFC14146 and EFC14280, and the 300 mg once every 4 weeks (q4w) regimen was evaluated following 24 weeks of 300 mg q2w treatment in Study EFC14280. All of these studies included an assessment of immunogenicity.

2.3.2. Pharmacokinetics

Bioanalytical methods

Bioanalytical assays used for the CRSwNP program have been employed previously during the bioanalysis of clinical study samples in the AD and asthma submissions.

Serum samples for quantitation of functional dupilumab (ie, dupilumab with 1 or both binding sites available for target IL-4Rα binding) in human serum were analysed using validated enzyme-linked immunosorbent assays (ELISAs) with a lower limit of quantitation (LLOQ) of functional dupilumab of 0.078 mg/L in undiluted human serum. The functional dupilumab concentration assay (R668-AV-13074-VA-01V1) used in the CRSwNP phase 2 ACT12340 and the phase 3 (EFC14146 and EFC14280) studies was submitted with the original AD application. Incurred sample reanalysis (ISR) for the functional dupilumab assay was performed in the ACT12340 study.

The ADA analysis of the ACT12340 study was conducted using the R668-AV-13089-VA-01V1 assay. A 2-assay approach (previously described in the asthma marketing application) using the ADA assay and the modified ADA assay was employed for the 2 pivotal CRSwNP phase 3 studies (EFC14146 and EFC14280). Assay cut points established for ADA assays were based on statistical methods recommended in appropriate guidelines (EMA Guideline, 2009) with the objective of demonstrating that the assay is suitable and reliable for the detection of ADA in patient sera.

The NAb analysis was only performed in the phase 3 studies, using the R668-AV-13112-01V2 assay which has been described in the asthma marketing application.

For the CRSwNP indication in adults, the to-be marketed dupilumab drug product is a liquid formulation at a concentration of 150 mg/mL, supplied in a 2 mL volume as a prefilled syringe to deliver a dose of 300 mg for subcutaneous (SC) administration. This formulation was approved as part of the original marketing application for atopic dermatitis (AD). Data demonstrating comparability of the approved commercial drug substance (DS) to the DS previously used in clinical development program has been submitted in the original marketing application for AD.

Across the Phase 2 and Phase 3 program in CRSwNP, blood levels of the type 2 inflammation biomarkers (thymus and activation-regulated chemokine [TARC], total IgE, eosinophil cationic protein [ECP] and periostin) were assessed as markers for disease activity/severity and to gain a better mechanistic understanding of dupilumab action. These same markers and eotaxin-3 were also assessed from nasal secretions to similarly gain an understanding of dupilumab's actions in the sino-nasal cavity. In addition, the dupilumab effect on leukotriene E4 (LTE4) in urine, a stable end product of the cysteinyl leukotriene pathway and a marker of activation of mast cells, involved in

type 2 inflammation in patients with CRSwNP and NSAID-ERD, was explored. Concentrations of ECP and IgE were measured using quantitative ImmunoCAP assays. Serum TARC and periostin were assayed with validated enzyme immunoassays. Blood eosinophil count was measured by haematology autoanalyzer. Urine LTE4 was quantified by LC/MS. Eotaxin-3 from nasal secretion was assayed with a validated immunoassay. Eotaxin-3 was measured in heparinized plasma with a validated enzyme immunoassay.

Chronic rhinosinusitis with nasal polyposis (CRSwNP), atopic dermatitis (AD), and asthma share many of the same underlying disease mechanisms as all 3 diseases are type 2 inflammation driven, with the tissue where this inflammation manifests as a disease differing. In addition, 59% of the CRSwNP patients enrolled in the pivotal program had comorbid asthma showing the significant overlap of the type 2 diseases. However, in response to the Agency's RSI, a developmental exercise was conducted to demonstrate selectivity of the functional dupilumab PK assay in serum samples from CRSwNP patients. The selectivity assessment was performed using baseline serum samples (Sa 01 to Sa 10; Table see below) from a dupilumab CRSwNP phase 3 clinical study. Samples were analyzed unspiked and spiked with 1.56 ng/mL (0.078 mg/L in neat serum) of dupilumab, which is the lower limit of quantification of the assay. No matrix interference was observed in the unspiked samples, as all ten samples were below the limit of quantification (BLQ). All ten patient samples spiked with 1.56 ng/mL of dupilumab demonstrated acceptable analyte recovery (%AR), with values ranging from 84% to 100%.

Table 2 Selectivity of the functional dupilumab assay in CRSwNP patient samples

	Unspiked Nasal Polyp Samples		Nasal Polyp Samples Spiked with 1.56 ng/mL of Dupilumab (0.078 mg/L in Neat Serum)				
Sample ID	MeanRLU	Mean Dupilumab Concentration (ng/mL)	Nominal Concentration (ng/mL)	Mean RLU	Mean Dupilumab Concentration (ng/mL)	CV% Dose	%AR
Sa01	10	BLQ	1.56	1266	1.35	3	87
Sa02	12	BLQ	1.56	1358	1.44	1	92
Sa03	16	BLQ	1.56	1319	1.4	12	90
Sa04	10	BLQ	1.56	1350	1.43	5	92
Sa05	13	BLQ	1.56	1433	1.51	0	97
Sa06	14	BLQ	1.56	1492	1.57	1	100
Sa07	12	BLQ	1.56	1412	1.49	2	96
Sa08	10	BLQ	1.56	1488	1.56	0	100
Sa09	11	BLQ	1.56	1226	1.32	0	84
Sa10	14	BLQ	1.56	1240	1.33	4	85

RLU=relative luminescence units

Pharmacokinetic data and analyses

Dupilumab concentrations were measured in the target CRSwNP population in one Phase 2 (Study ACT12340) and 2 pivotal Phase 3 studies (Studies EFC14146 and EFC14280) using sparse sampling (samples collected at predose, during treatment, and the follow up period). Descriptive statistics were used to summarize the concentration data over time in the individual CRSwNP studies. Dupilumab concentrations determined in the CRSwNP population were also compared to the dupilumab concentrations in the AD and asthma populations as well as in healthy subjects.

To assess the E-R or PK/PD relationship for key efficacy endpoints in the CRSwNP population, descriptive E-R analysis by exposure quartiles for data from the pivotal Phase 3 studies (EFC14146 and EFC14280), as well as model-based PK/PD analyses (Study POH0687) using these pooled Phase 3 data were performed.

- Collection of PK and PD data from the phase 2 and phase 3 studies

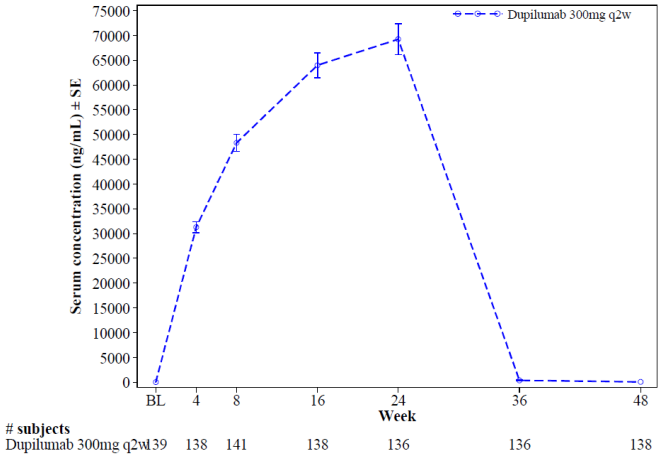
PK and PD data were collected from the phase 2 (ACT12340) and phase 3 studies (EFC14146, EFC14280) submitted in this application and are described below separately.

A) Pharmacokinetic Results (study EFC14146):

Blood samples for measurements of functional dupilumab concentration were taken at baseline (Day 1), Week 4, Week 8, Week 16, Week 24 (EOT), Week 36, and Week 48. Samples for the detection of ADA, NAb, and type 2 PD biomarkers (TARC, periostin, IgE) were collected at the time points specified. Urine samples were collected for measurement of LTE4.

In patients receiving dupilumab treatment, pre-dose concentrations were below the lower limit of quantitation (LLOQ). Following SC administration of dupilumab 300 mg q2w, the mean serum trough dupilumab concentration increased to 31.3 mg/L at Week 4 and C_{trough} increased over time to Week 24 with mean (SD) C_{trough} at 69.2 (36.9) mg/L. Following discontinuation of study treatment mean trough concentration decreased to 0.356 mg/L at Week 36.

Figure 1 Serum concentration (ng/mL) of dupilumab over time - PK population

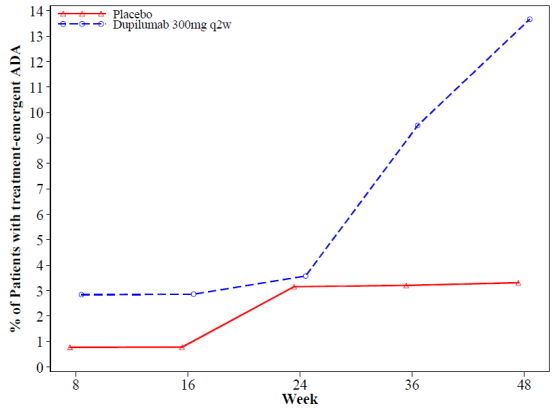


Mean trough concentrations of dupilumab increased over time to 69.2 mg/L at Week 24.

Immunogenicity Results:

15.4% of dupilumab treated patients showed treatment-emergent ADA responses at at least one time point compared to 5.3% of placebo patients. The majority of ADA responses were low titer (<1000), with 1 patient in the dupilumab group having a moderate titer response (1000 to 10 000). One patient, who was in the placebo group received one dose of dupilumab by error, had a high titer response (>10 000) and was included in the dupilumab 300 mg SC q2w arm in the immunogenicity related analyses. Persistent ADA responses occurred in 3.5% of dupilumab patients compared with 1.5% in placebo patients. There was an overlap in the individual exposure across patients of different ADA status with that of ADA negative patients.

Figure 2 Percentage of patients with treatment-emergent ADA positive response at each visit - ADA population



# subjects					
Placebo	130	129	127	125	121
Dupilumab 300mg q2w	141	140	140	137	139

The proportion of patients with a treatment-emergent ADA positive response by visit ranged from 2.8% to 3.6% in the dupilumab 300 mg q2w and 0.8% to 3.1% in the placebo group between Weeks 8 and 24. The proportion of patients with a treatment-emergent ADA positive response increased to 9.5% to 13.7% in the dupilumab 300 mg q2w group but remained at 3.2 to 3.3% in the placebo group post-treatment period. Samples positive in the ADA assay were further characterized for the presence of NAbs. 10.5% of patients in the dupilumab group and 0% in the placebo group were positive in the NAb assay. Among the 15 NAb positive patients, a persistent ADA response was observed in 4 patients (all in the dupilumab group). Among the NAb positive patients, high titer ADA responses were observed in only 1 patient who was administered one dose of dupilumab by error.

Table 3 Summary of ADA incidence - ADA population

	Placebo (N=132)	Dupilumab 300mg q2w (N=143)
Patients with Pre-existing immunoreactivity	2 (1.5%)	1 (0.7%)
Patients with treatment-emergent response	7 (5.3%)	22 (15.4%)
Persistent response	2 (1.5%)	5 (3.5%)
Transient response	4 (3.0%)	9 (6.3%)
Indeterminate response	1 (0.8%)	8 (5.6%)
Peak post-baseline titer		
Number	7	22
Low (<1000)	7/132 (5.3%)	20/143 (14.0%)
Moderate (1000-10000)	0/132	1/143 (0.7%)
High (>10000)	0/132	1/143 (0.7%)[a]
Patients with treatment-boosted response	0	0

PGM=PRODOPS/SAR231893/EFC14146/CSR/REPORT/PGM/pk_ada_cat_a_t.sas OUT=REPORT/OUTPUT/pk_ada_cat_sub_a_t_i.rtf (02DEC2018 - 2:37)

a Includes one patient with ADA treatment-emergent response in the placebo group who was administered one dose of dupilumab

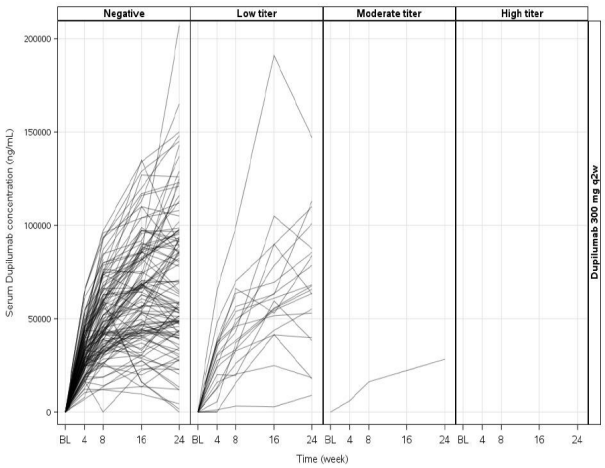
Analyses regarding association between ADAs and adverse events, efficacy and PK

Patients with treatment-emergent or treatment-boosted ADA responses were grouped and referred to as ADA-positive patients. Patients who were ADA negative at all times or had pre-existing immunoreactivity were also grouped together and referred to as ADA-negative patients.

- ADA and pharmacokinetics

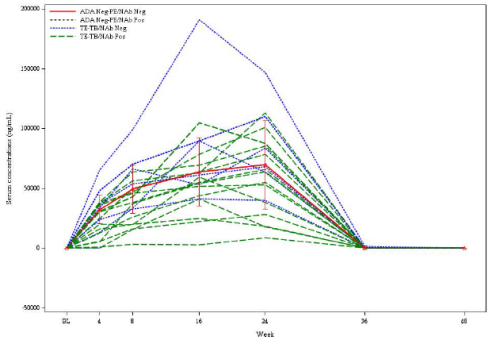
A trend of lower mean dupilumab exposure was seen in ADA-positive patients compared to ADA-negative patients. However, there was substantial overlap in individual dupilumab exposure regardless of ADA status.

Figure 3 Spaghetti plot of Dupilumab concentration over time (on treatment) by ADA titer category - PK population



The individual dupilumab concentrations in ADA-positive patients were generally within the exposure range observed in ADA-negative patients, except for one patient with a moderate titer ADA response (1000 to 10 000). The dupilumab exposure was lower for this patient with moderate titer ADA.

Figure 4 Serum concentrations of dupilumab over time by ADA and NAb status of patients in the dupilumab 300mg q2w group - ADA population



BL=Baseline
ADA Neg-PE/NAb Neg: (ADA negative at all times OR pre-existing immunoreactivity) AND NAb negative
ADA Neg-PE/NAb Pos: (ADA negative at all times OR pre-existing immunoreactivity) AND NAb positive
TE-TB/NAb Neg: (Treatment-emergent OR treatment-boosted) AND NAb negative
TE-TB/NAb Pos: (Treatment-emergent OR treatment-boosted) AND NAb positive

Possible effects of NAb positivity on dupilumab PK were assessed. In line with the results described above, a slight lower mean dupilumab exposures was observed for the treatment-emergent ADA response patients with Nab positive status. However, an overlap in individual dupilumab exposure regardless of Nab status was seen.

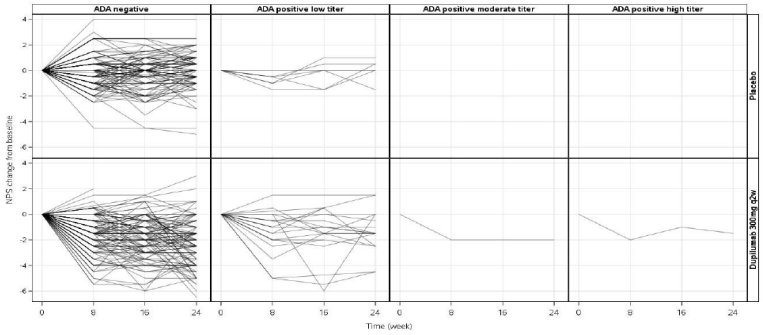
- ADA and efficacy

The relationship between ADA and clinical response measured by change from NPS and NC at week 24 (co-primary endpoints) was investigated in treatment-emergent ADA positive patients.

Of note, the evaluation of the association of a treatment-emergent ADA response with these efficacy assessments is based on a small population (N=22 ADA-positive patients for the dupilumab group).

LS mean change from baseline to Week 24 in NPS was -1.11 for the ADA-positive and -2.02 and ADA-negative patients. LS mean change from baseline to Week 24 in NC was -1.39 for the ADA-positive and -1.33 and ADA-negative patients.

Figure 5 Spaghetti plot of bilateral NPS over time (on treatment) by peak post-baseline ADA titer categories - ADA population



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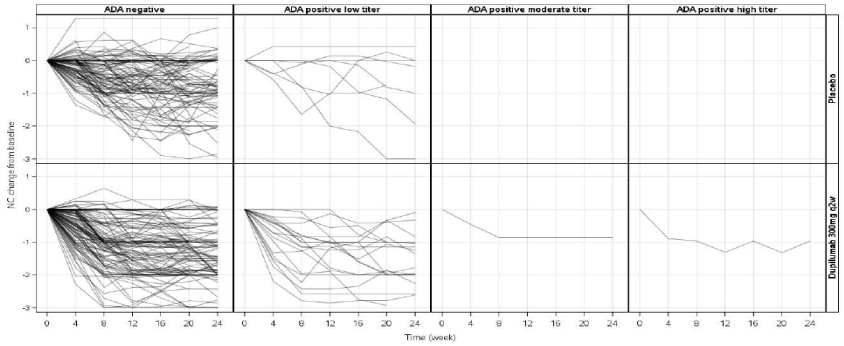
ADA high titer category includes one patient with ADA treatment-emergent response in the placebo group who was administered one dose of dupilumab

Figure 6 Spaghetti plot of nasal congestion/obstruction over time (on treatment) by peak postbaseline ADA titer categories - ADA population



PGM=PRODOPS/SAR231893/EFC14146/CSR/EXPLO/PGM/a_pk_eff_ada_trt_a_g.sas OUT=EXPLO/OUTPUT/a_pk_eff_ada_nc_trt_a_g_i.rtf (05DEC2018 - 1:57)
ADA high titer category includes one patient with ADA treatment-emergent response in the placebo group who was administered one dose of dupilumab

- ADA and adverse events

Of note, similar to the evaluation of the association of a treatment-emergent ADA response with the efficacy co-primary endpoints, there was only a limited number of patients with an ADA response. No apparent imbalance was seen in TEAE incidence in the few ADA-positive patients (N=29) compared with the ADA-negative patients (N=246). Of the 29 patients who were ADA-positive, 21 patients had TEAEs, with no apparent pattern or increase in TEAE incidence in the ADA-positive patients compared with the ADA-negative patients. Three ADA-positive patients had events that were considered SAEs (uterine polyp, carpal tunnel syndrome, EGPA) and 1 ADA-positive patient had TEAEs that led to permanent treatment discontinuation (accidental overdose on Day 40 and ligament sprain on Day 41). For each of these patients, there was no temporal relationship between the AE and the ADA positive response. Analysis of the potential impact of NAb on TEAEs was also limited by the small number of patients with a positive NAb response. Of the 15 patients with a NAb response across both treatment groups, 10 patients had at least one TEAE.

- Analysis of hypersensitivity reactions and other adverse events of interest by ADA status

One of 29 ADA-positive patients had an SAE of EGPA (eosinophilic granulomatosis with polyangiitis). This SAE occurred at Day 8 and lead to treatment discontinuation. This 61-year-old female patient had a history of asthma, allergic rhinitis, autoimmune thyroid disease, and hypertension and Eosinophilia, that increased to 2.42 Giga/L at Day 1 (prior to 1st and last IMP) and was reported as an AE of severe intensity on Day 7 (4.89 Giga/L). The patient was ADA negative around the time of the event, and had a low-titer (30) transient treatment-emergent response on Day 112.

- Analysis of injection site reactions by ADA status

Of the 29 ADA-positive patients across both treatment groups, no patients in the dupilumab and 1 patient (14.3%) in the placebo group had an event defined as injection site reaction. Among the 246 ADA-negative patients 29 were reported with an injection site reaction (10.7% in the dupilumab group and 12.8% in the placebo group). However, due to the small numbers of patients no meaningful conclusion can be drawn.

In this patient population the incidence of treatment-emergent ADA was 15.4% in the dupilumab group. The relationship between ADA and clinical response measured by change from NPS and NC at week 24 (co-primary endpoints) was evaluated. Only a small difference in NPS and no difference in NC results between ADA positive and negative patients. However, this evaluation was based on a small number of patients (N=22 ADA-positive patients for the dupilumab group). ADA formation did not appear to correlate with any safety findings. Additionally, no difference was seen in number of the reported injection side reaction between the dupilumab and placebo treatment group.

<u>B) Pharmacokinetic Results from EFC14280</u>

At the time of the data cut-off for the CSR (29 August 2018) PK data for Week 52 were available for approximately 70% of patients in the study. Results are described below:

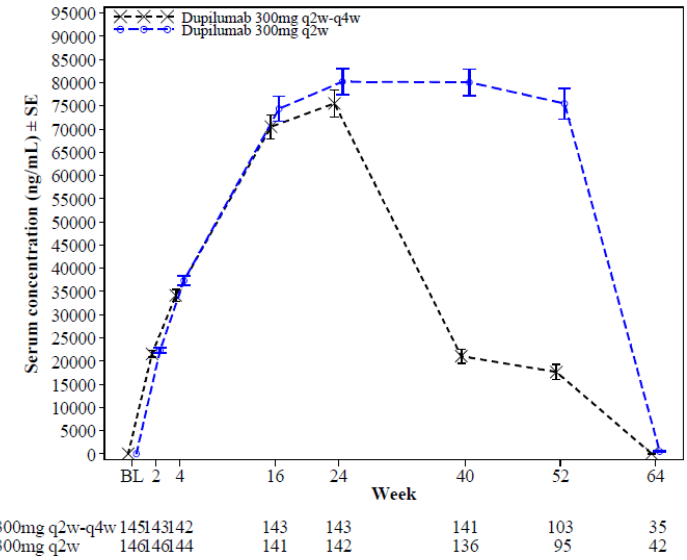
Functional dupilumab concentrations in serum were measured at baseline (Day 1) and Weeks 2, 4, 16, 24, 40, 52 (EOT), and 64 (EOS). Pre-dose concentrations were below the lower limit of quantitation (LLOQ). Blood samples for measurements of functional dupilumab concentration, detection of ADA, and type 2 PD biomarkers (TARC, periostin, IgE) were collected at time points specified as well as urine LTE4.

Following the administration of dupilumab 300 mg q2w, the mean trough dupilumab concentration were 22.3 mg/L for the dupilumab 300 mg q2w and 21.5 mg/L for the 300 mg q2w-q4w groups at Week 2.

In treatment Arm A (300 mg q2w) C_{trough} appeared to reach steady state by Week 16 and was sustained at the steady-state levels throughout the treatment period. At steady state, the mean trough concentration was 74.4 to 80.2 mg/L. Accumulation, as assessed by trough concentration following the twelfth dose compared to trough concentration after the first dose, was 3.60-fold at 300 mg q2w. For the 300 mg q2w−q4w group, the PK profile was similar to 300 q2w group from baseline to Week 24. After the switch from the 300 mg q2w to 300 mg q4w dosing regimen at Week 24, mean trough concentration decreased from 75.5 mg/L at Week 24 to 17.6 mg/L at Week 52. The mean trough concentration increased in a greater than dose-proportional manner at Week 52 (4.29-fold [17.6 versus 75.5 mg/L] for a 2-fold dose increase from 300 mg q4w to 300 mg q2w).

More patients in the dupilumab 300 mg q2w-q4w group (8.7%) had steady-state concentrations at the end of the 52-week treatment that were below the limit of quantitation (0.078 mg/L) than in the 300 mg q2w treatment group (1.8%). Some patients may not have reached full saturation of the target-mediated elimination at the steady-state exposure of 300 mg q4w.

Figure 7 Serum concentration (ng/ml) of dupilumab over time - PK population



Immunogenicity Results:

In the full cumulative analysis, treatment-emergent ADA responses were observed in 5.4% of patients in the dupilumab 300 mg q2w group, 12.2% of patients in the dupilumab 300 mg q2w-q4w group, and 4.0% of the placebo group. The majority of ADA responses were low titer (<1000), with 3 patients having a high titer response (>10 000) (2 patients in the dupilumab 300 mg q2w group and 1 patient in the dupilumab 300 mg q2w-q4w group). Persistent ADA responses as defined in SAP (5.3.5.1 Study EFC14280 [16-1-9-sap]) occurred in 2.7% (4/148) of patients in the 300 mg q2w group and 4.1% (6/148) of patients in the 300 mg q2w-q4w group compared with 0.7% (1/149) observed in the placebo group.

Table 4 Summary of ADA incidence - ADA population

		Dupilumab	
	Placebo (N=149)	300mg q2w-q4w (N=148)	300mg q2w (N=148)
Patients with Pre-existing immunoreactivity	4 (2.7%)	4 (2.7%)	4 (2.7%)
Patients with treatment-emergent response	6 (4.0%)	18 (12.2%)	8 (5.4%)
Persistent response	1 (0.7%)	6 (4.1%)	4 (2.7%)
Transient response	5 (3.4%)	3 (2.0%)	4 (2.7%)
Indeterminate response	0	9 (6.1%)	0
Peak post-baseline titer			
Number	6	18	8
Low (<1000)	4/149 (2.7%)	17/148 (11.5%)	6/148 (4.1%)
Moderate (1000-10000)	2/149 (1.3%)	0/148	0/148
High (>10000)	0/149	1/148 (0.7%)	2/148 (1.4%)
Patients with treatment-boosted response	1 (0.7%)	0	0

PGM=PRODOPS/SAR231893/EFC14280/CSR_2/REPORT/PGM/pk_ada_cat_a_t.sas OUT=REPORT/OUTPUT/pk_ada_cat_sub_a_t_1.rtf (01FEB2019 - 3:56)

The proportion of patients with a treatment-emergent ADA by visit ranged from 2.1% to 4.1% in the dupilumab 300 mg q2w group, 3.4% to 5.6% in the dupilumab 300 mg q2w-q4w group, and 0.7% to 3.0% in the placebo group between Weeks 8 and 52.

The differences between treatment groups observed in the proportion of patients with a treatment-emergent ADA at Week 52 (3.5% and 5.6% for the dupilumab 300 mg q2w and q2w-q4w groups, respectively, versus 3.0% for the placebo group) were amall. However, the proportion of patients

with a treatment-emergent ADA at Week 64 in the post treatment period was 2.2% and 11.4% for the dupilumab 300 mg q2w and q2w-q4w groups, respectively, versus 1.7% for the placebo group.

Further characterization was performed regarding the presence of Nabs.

In the full cumulative analysis, the proportion of patients positive in the NAb assay was 3.4% in the 300 mg q2w group, 11.5% in the 300 mg q2w-q4w group, and 2.0% in the placebo group. Among the 25 NAb positive patients, a persistent ADA response was observed in 9 patients, of whom 2 were in the 300 mg q2w group, 6 were in the 300 mg q2w-q4w group, and 1 was in the placebo group. All 3 patients with high titer ADA responses were NAb positive.

Table 5 Summary of neutralizing antibody (NAb) Status - ADA population

		Dupilumab	
	Placebo (N=149)	300mg q2w-q4w (N=148)	300mg q2w (N=148)
Patients with positive NAb [a]	3 (2.0%)	17 (11.5%)	5 (3.4%)
Persistent response	1 (0.7%)	6 (4.1%)	2 (1.4%)
Peak post-baseline ADA titer			
High (>10000)	0	1 (0.7%)	2 (1.4%)

[a] NAb positive patients are defined as patients with at least one post-baseline ADA classified as neutralizing positive.
Note: Percentages under category of 'NAb positive patients' are calculated with the denominator of number of NAb positive patients.
PGM=PRODOPS/SAR231893/EFC14280/CSR_2/REPORT/PGM/pk_ada_catsum_a_t.sas
OUT=REPORT/OUTPUT/pk_ada_catsum_sub_a_t_i.rtf (01FEB2019 - 4:00)

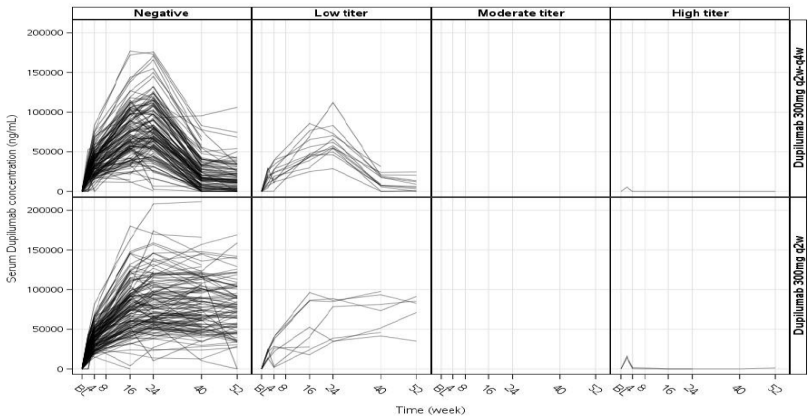
Analyses of any associations between ADA and adverse events, efficacy, and PK

Similar to study EFC 14146 patients with treatment-emergent or treatment-boosted ADA responses were grouped and referred to as ADA-positive patients. Patients who were ADA negative at all times or had pre-existing immunoreactivity were also grouped together and referred to as ADA-negative patients.

- ADA and pharmacokinetics

A trend of lower mean dupilumab exposure was observed in ADA-positive patients compared to that in ADA-negative patients.

Figure 8 Spaghetti plot of dupilumab concentration over time (on treatment) by ADA titer category –PK population



However, a substantial overlap in individual dupilumab exposure regardless of ADA status was seen and individual dupilumab concentrations in ADA-positive patients were generally within the exposure range observed in ADA-negative patients, except for 3 patients with high titer ADA

response (>10 000). These patients with high titer ADA had treatment-emergent persistent ADA response, were ADA positive and NAb positive from Week 8 throughout Week 52. Significant lower dupilumab exposure was observed for these 3 patients, with dupilumab concentrations that decreased from Week 4 onward and then stayed below or close to the limit of quantitation (BLQ) despite continued treatment with dupilumab.

Figure 9 Summary of serum concentrations of dupilumab over time by ADA and NAb status of patients in the Dupilumab 300mg q2w group- ADA population

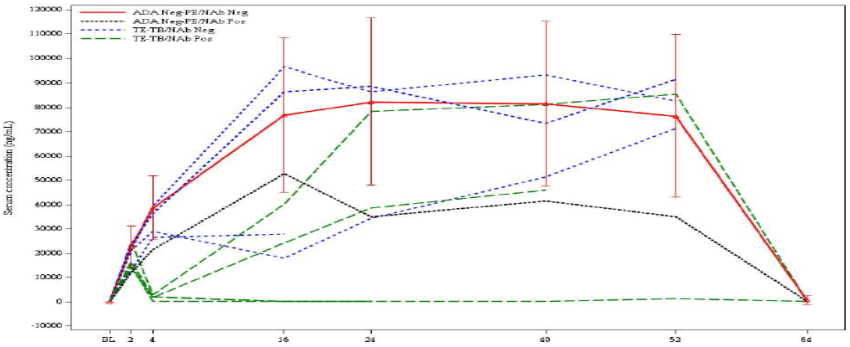
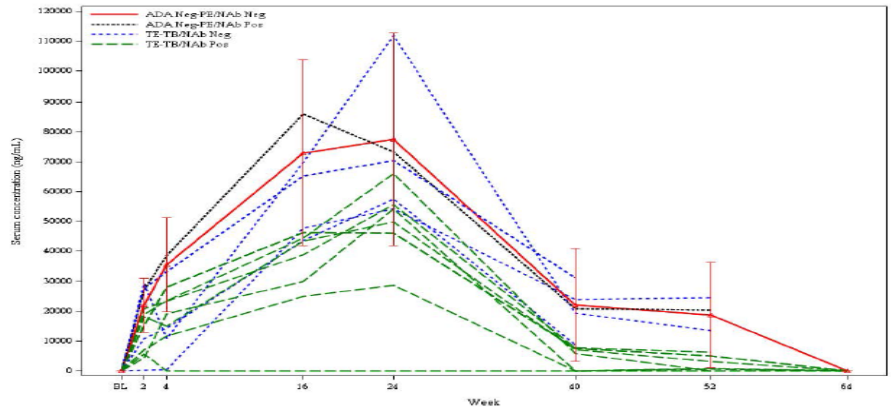


Figure 10 Summary of serum concentrations of dupilumab over time by ADA and NAb status of patients in the Dupilumab 300mg q2w-q4w group- ADA population



BL=Baseline
ADA Neg-PE/NAb Neg: (ADA negative at all times OR pre-existing immunoreactivity) AND NAb negative
ADA Neg-PE/NAb Pos: (ADA negative at all times OR pre-existing immunoreactivity) AND NAb positive
TE-TB/NAb Neg: (Treatment-emergent OR treatment-boosted) AND NAb negative
TE-TB/NAb Pos: (Treatment-emergent OR treatment-boosted) AND NAb positive

A slightly lower mean dupilumab exposure was observed for the treatment-emergent ADA response patients with NAb positive status. However, there was an overlap in individual dupilumab exposure regardless of NAb status, only those patients with high titer responses resulted in substantially reduced exposure.

- ADA and efficacy

The relationship between ADA and clinical response (co-primary endpoints: change from baseline in NPS and change from baseline in NC score at Week 24) was investigated in ADA-positive patients.

It has to be noted that the evaluation is based on numerical imbalance between ADA-positive patients (N=25) compared with ADA-negative patients (N = 268) for the pooled 300 mg q2w group [Arm A+B]).

The LS mean change from baseline to Week 24 in NPS was -1.35 for the ADA-positive and -1.73 for the ADA-negative patients, while the LS mean change from baseline to Week 24 in NC was -0.98 for the ADA-positive and -1.27 for the ADA-negative patients.

Table 6 Change from baseline in bilateral NPS at Week 24 by ADA status - ADA population

	Placebo (N=151)	Dupilumab 300mg q2w (N=294)
ADA Positive Patients (treatment-emergent or treatment-boosted)		
Baseline		
Number	7	25
Mean (SD)	5.64 (0.80)	6.58 (1.20)
Median	6.00	6.50
Q1 : Q3	5.00 : 6.50	5.50 : 8.00
Min : Max	4.5 : 6.5	4.0 : 8.0
Change from baseline at Week 24		
Number	5	25
Mean (SD)	0.20 (1.89)	-1.64 (1.90)
Median	-0.50	-2.00
Q1 : Q3	-1.00 : 0.00	-3.00 : 0.00
Min : Max	-1.0 : 3.5	-5.5 : 2.0
LS Mean (SE) [a]	-0.10 (0.83)	-1.35 (0.43)
LS Mean Diff vs. placebo (95% CI) [a]		-1.25 (-2.91, 0.41)
P-value vs. placebo [a]		0.1390
ADA Negative Patients (Pre-existing immunoreactivity or negative ADA at all times)		
Baseline		
Number	143	268
Mean (SD)	5.98 (1.23)	6.14 (1.21)
Median	6.00	6.00
Q1 : Q3	5.50 : 7.00	5.50 : 7.00
Min : Max	2.0 : 8.0	1.5 : 8.0

[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the co-primary endpoints.
[b] At least one post-baseline ADA measurement classified as neutralizing positive.
[c] All ADA measurements are neutralizing negative
Note: Low titer: < 1,000; Moderate titer: 1,000 - 10,000; High titer: > 10,000

For the 3 patients with high titer ADA (>10 000; 2 patients in the 300 mg q2w group and 1 patient in the 300 mg q2w-q4w group), dupilumab concentrations were consistently reduced to the below detection level and the results in NPS did not show a sustained or consistent improvement throughout the study. Additionally, 2 of these 3 patients had a TEAE of nasal polyps, consistent with lack of efficacy. Nasal congestion/obstruction (NC) showed a sustained improvement in 1 of the 3 patients.

- ADA and adverse events

Analyses of TEAEs by MedDRA primary SOC and PT were performed for subgroups of patients based on ADA response status. Additionally, focused analyses evaluated any potential association of hypersensitivity and serious or severe (lasting more than 24 hours) injection site reactions by ADA response status.

33 patients who were ADA-positive (8 in the dupilumab 300 mg q2w, 18 in the 300 mg q2w-q4w, and 7 patients in the placebo group). Of these patients 28 had TEAEs. However, no apparent pattern or increased incidence was identified. TEAEs that occurred in more than one patient in the either dupilumab group included nasopharyngitis, sinusitis, bronchitis, urinary tract infection, headache, nasal polyps, asthma, nasal discomfort, cough, arthralgia, injection site reaction, injection site bruising, accidental overdose, and fall (in the 300 mg q2w-q4w group).

Four patients with a treatment-emergent ADA response had events that were considered SAEs and/or had a TEAE that resulted in permanent treatment discontinuation. One patient in the 300 mg q2w group with lupus-like syndrome, two patients in the 300 mg q2w/q4w group with back pain and EGPA and one patient in the placebo group with miscarriage of partner pregnancy. There was no temporal relationship between the AE and the ADA positive response.

The 3 patients with high ADA titer (>10 000) experienced at least one TEAE during the study, none of which were serious or led to permanent treatment discontinuation. However, 2 these patients had the TEAE of worsening of nasal polyps.

Analysis of the potential impact of NAb on TEAEs was limited by the small number of patients with a positive NAb response. Of the 17 patients with a NAb response across the 3 treatment groups (5, 9, and 3 patients in the dupilumab 300 mg q2w, 300 mg q2w-q4w, and placebo groups respectively), 14 patients had at least one TEAE, with no apparent pattern or increase in TEAE incidence. TEAES that occurred in more than one patient included nasopharyngitis, sinusitis, headache, nasal polyps, injection site bruising, and accidental overdose.

Since the initial cut-off date, 7 additional patients with a positive NAb response had at least one TEAE, all of them in the dupilumab 300 mg q2w-q4w group. Cumulatively, of the 25 patients with a positive NAb response across the 3 treatment groups (5, 17, and 3 patients in the dupilumab 300 mg q2w, 300 mg q2w-q4w, and placebo groups respectively), 21 patients had at least one TEAE, with no apparent pattern or increase in TEAE incidence.

- Analysis of hypersensitivity reactions and other adverse events of interest by ADA status

None of the 27 ADA-positive patients had a potential hypersensitivity reaction. One ADA-positive patient had EGPA. This patient had been assigned to the placebo group, but accidently received a single dose of 300 mg dupilumab on Day 30, more than 300 days prior to the episode of EGPA.

One patient (dupilumab 300 mg q2w-q4w group) had a serious or severe injection site reaction lasting more than 24 hours but was ADA negative throughout the study. 4 of the 27 ADA-positive patients (1 [12.5%] in the dupilumab 300 mg q2w and 3 [25.0%] in the 300 mg q2w-q4w group and 0 in the placebo group) had an event coded to the HLT of injection site reaction. In comparison, 66 of 418 of ADA-negative patients with an injection site reaction (15.0% in the dupilumab 300 mg q2w, 18.4% in the 300 mg q2w-q4w group, and 14.1% in the placebo group). None of these events were considered serious or led to permanent treatment discontinuation.

Overall, the observed incidence of treatment-emergent ADA was low and no meaningful differences between treatment groups were observed in patients with a treatment-emergent ADA response at Week 52 (4.0% for dupilumab 300 mg q2w, 4.8% for dupilumab q2w-q4w and 4.8% for the placebo group).

The majority of the ADA responses had low ADA titer. ADA formation did not appear to correlate with any safety findings. For the 3 patients with high titer ADA a reduced dupilumab concentration in serum was seen and NPS and NC did not show a sustained improvement throughout the study.

It has to be noted that the evaluation of relationship between ADA and clinical response was based on small number of ADA-positive patients (N=19) compared with the ADA-negative patients (N = 274).

PK parameters across studies in patients with CRSwNP

Dupilumab steady-state exposure was similar across the studies with various dupilumab treatment durations. The Pop PK model estimates were consistent with the observed values for Ctrough.

Table 7 Mean (SD) steady-state exposure of dupilumab in patients with CRSwNP (Studies ACT12340, EFC14146, and EFC14280)

Study identifier	Dose		$C_{max,ss}$ (mg/L)	$AUC_{\tau,ss}$ (mg•day/L)		$C_{trough,ss}$ (mg/L)	
		N	Predicted[b]	Predicted[b]	Predicted[b]	N	Observed
ACT12340[a]	300 mg qw	28	177 (52.2)	1210 (360)	165 (49.9)	29	176 (52.4)
EFC14146	300 mg q2w	135	86.5 (31.5)	1100 (424)	65.4 (28.0)	136	69.2 (36.9)
EFC14280	300 mg q2w	135	102 (35.1)	1307 (472)	79.3 (31.4)	95	75.5 (33.5)
	300 mg q2w–q4w	141	46.5 (19.6)	929 (483)	17.9 (13.7)	103	17.6 (17.4)

Abbreviation: N: number of patients; $AUC_{\tau,ss}$: Area under the concentration time curve over the dosing interval (τ) at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; qw: once every week; q2w: every two weeks; q4w: every four weeks; NA: not applicable; SD: standard deviation

a Dose regimen of 300 mg qw with a loading dose of 600 mg in ACT12340

b Predicted: summary statistics of post hoc estimates of exposure parameters based on the CRSwNP Pop PK model in Study POH0611

$AUC_{\tau,SS}$ = AUC[Week 15 – Week 16] for 300 mg qw from Study ACT12340

$AUC_{\tau,SS}$ = AUC[Week 22 – Week 24] for 300 mg q2w from Study EFC14146

$AUC_{\tau,SS}$ = AUC[Week 50 – Week 52] and AUC[Week 48 – Week 52] for 300 mg q2w and 300 mg q4w from Studies EFC14280

$C_{trough,ss}$ represents the mean trough concentration at Week 16 for Study ACT12340, and Week 24 for Study EFC14146, Week 52 for Study EFC14280

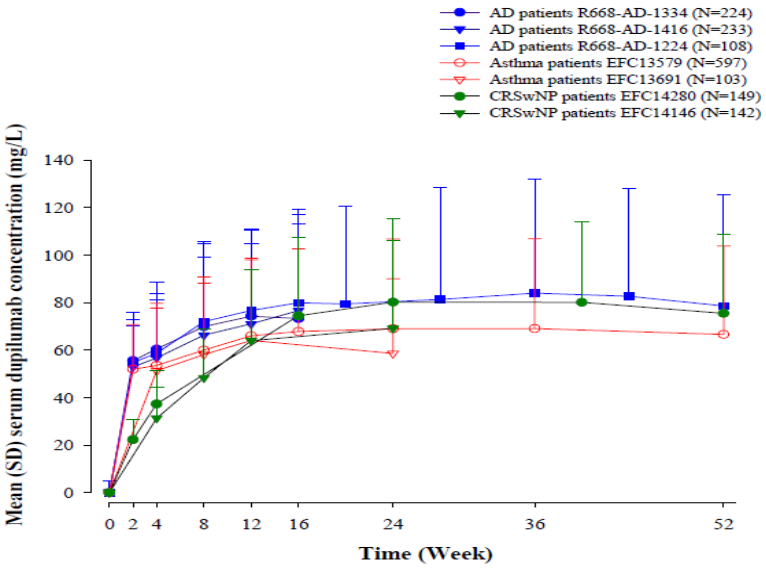
Dupilumab PK comparison between CRSwNP and other patient populations

The baseline demographic characteristics of adult patients with CRSwNP, asthma and AD across the 3 clinical programs were similar. Dupilumab PK profiles in CRSwNP, asthma and AD patient populations were compared descriptively and via independent Pop PK analyses (Studies POH0611, POH0530, and REGN668MX16103).

The observed concentration-time profiles in patients with CRSwNP are similar across the CRSwNP studies and similar to the asthma and AD populations except the less rapidly increased concentrations due to the absence of a loading dose in patients with CRSwNP.

Following an initial SC dose of 300 mg in patients with CRSwNP and 600 mg in patients with AD and asthma, dupilumab reached Cmax (mean ± SD) of 30.5±9.39 mg/L and 70.1±24.1 mg/L, respectively. The observed dupilumab steady-state exposure (Ctrough) showed a high degree of similarity across CRSwNP, asthma and AD patient populations with various dupilumab treatment durations.

Figure 11 Mean (SD) trough concentration-time profiles of dupilumab at 300 mg q2w in patients with CRSwNP (without a loading dose) and asthma and AD (with a loading dose of 600 mg)



Additionally, the similarity in the PK of dupilumab between CRSwNP, asthma, and AD populations is supported by the results of the Pop PK analysis conducted separately for the 3 populations.

Table 8 Comparison of Pop PK model estimates of key PK parameters between CRSwNP, asthma and AD populations

PK Parameters	CRSwNP population	Asthma population	AD population
Typical value of F_{sc} (%)	0.628	0.61	0.64
Typical value of K_a (1/day)	0.250	0.263	0.306
Typical value of K_e (1/day)	0.0367	0.0418	0.0477
Typical value of V_{ss} (L)	4.91	4.37	4.60
Typical value of CL (L/day)	0.113	0.115	0.131
Typical value of V_{max} (mg/L/day)	1.16	1.39	1.07
Typical value of time to steady state[a]	16 weeks	8 weeks	10 weeks
Typical value of wash-out time from last dose at steady-state[a]	12 weeks	11 weeks	10 weeks
Typical value of $C_{trough,ss}$[a]	74.1 mg/L	67.8 mg/L	76.2 mg/L
Typical value of $C_{max,ss}$[a]	95.0 mg/L	85.2 mg/L	99.2 mg/L

Abbreviation: CL: linear clearance; F_{sc}: bioavailability K_a: absorption rate constant; K_e: linear elimination rate constant; V_{max}: maximum target-mediated rate of elimination; V_{ss}: volume of distribution at steady state (sum of central and peripheral compartment volume)

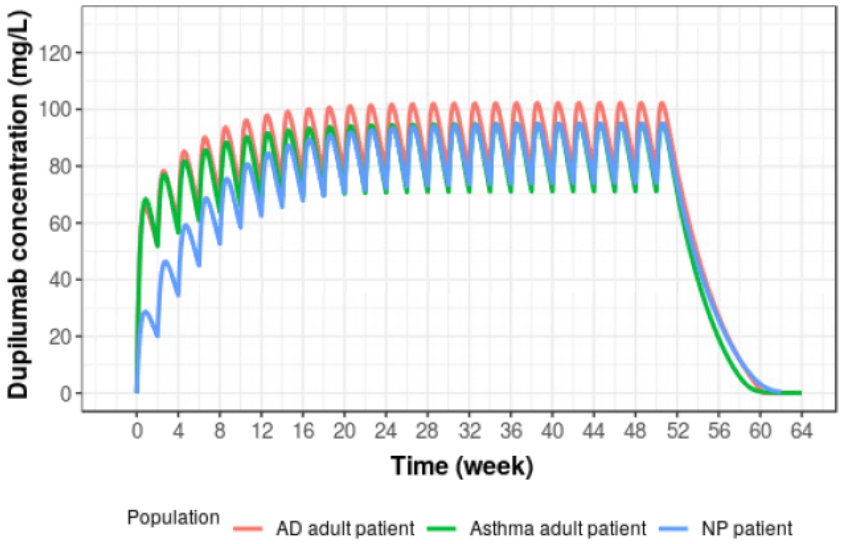
a Dose regimen of 300 mg q2w with a loading dose of 600 mg in asthma and AD populations only.

Source document: 5.3.3.5 Study POH0611 report of CRSwNP Pop PK analysis, in the subsequent marketing application for asthma, 5.3.3.5 Study POH0530 report of asthma Pop PK analysis and, in the original marketing application submission for AD, 5.3.3.5 REGN668-MX-16103 report of AD pop PK analysis.

Dupilumab concentration-over-time profiles in a typical CRSwNP, asthma or AD patient, as predicted from the respective CRSwNP, asthma, and AD Pop PK models, are comparable.

The main sources of variability of dupilumab PK identified in each population and the magnitude of the covariate effects indicate that body weight is the most influential factor on dupilumab PK. Other covariates identified as being statistically significant have shown no meaningful impact.

Figure 12Comparison of dupilumab typical concentration-time profiles at 300 mg q2w in patients with CRSwNP (without a loading dose) and asthma and AD (with a loading dose of 600 mg) as predicted by CRSwNP, asthma, and AD Pop PK models



The typical profile simulation was conducted using CRSwNP, asthma and AD Pop PK models for a typical Caucasian adult with CRSwNP, asthma or AD, respectively with demographics described as follows: weight of 75 kg (79 kg for CRSwNP), albumin of 45 g/L, body mass index (BMI) of 25.1 kg/m^2, creatinine clearance normalized to body surface area (CLCRN) of 111 mL/min/1.73 m^2, and eczema area severity index (EASI) of 29.5 (AD only) and negative ADA (median values of the covariates for the respective populations).

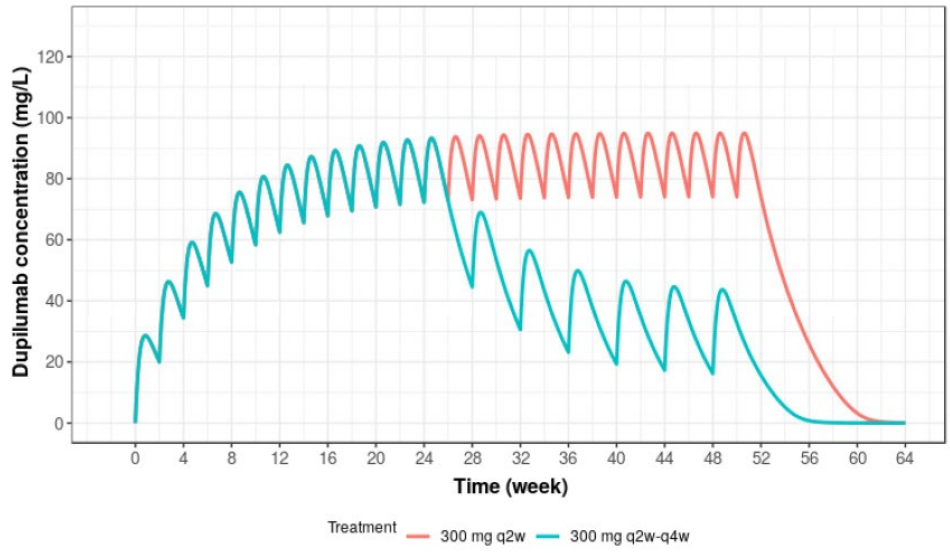
Steady-state and accumulation

In the Phase 2a CRSwNP Study ACT12340, dupilumab concentrations increased to a mean value of 76.3 mg/L at Week 2 after administration of a 600 mg loading dose for the 300 mg qw regimen. The concentrations continued to increase to a mean steady state (Ctrough) level of 166 mg/L by Week 12.

In the pivotal Phase 3 studies (EFC14146 and EFC14280) no loading dose was administered. The 300 mg q2w dosing regimen resulted in a mean dupilumab trough concentration of 21.5−22.3 mg/L at Week 2 and a mean steady-state trough level of 69.2−80.2 mg/mL at Week 24. The steady state Ctrough was achieved by Week 16 and was maintained up to 52 weeks. These results indicate the lack of a time-dependent change in dupilumab PK.

Based on the CRSwNP Pop PK model, the median time to steady-state was 16 weeks for 300 mg q2w without, which is longer than AD and asthma studies where a 600 mg loading dose was used. When switched from 300 mg q2w to 300 mg q4w at Week 24, the model predicts that a new steady state was achieved after an additional 24 weeks.

Figure 13 Comparison of typical concentration-time profiles of dupilumab at 300 mg q2w and 300 mg q2w−q4w predicted by CRSwNP Pop PK models



Note: The typical profile simulation was conducted using CRSwNP, Pop PK models for a typical Caucasian adult CRSwNP with weight of 79.0 kg.

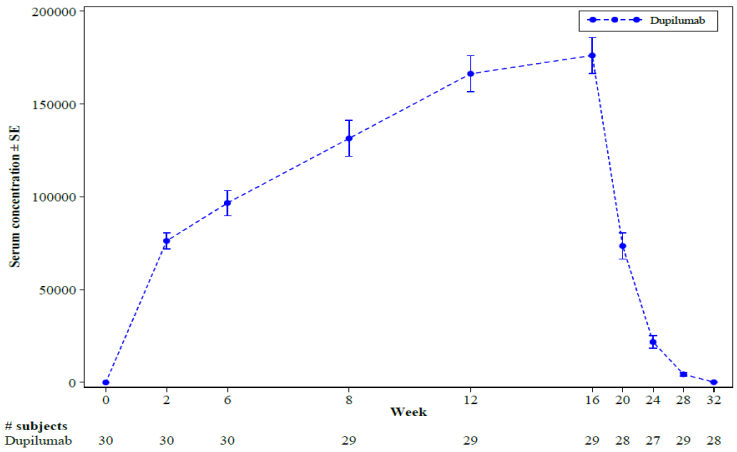
The dupilumab drug concentration data showed that more patients in the 300 mg q2wq4w regimen (8.7%) had steady-state concentrations that were below the limit of quantitation (0.078 mg/L) than those in the 300 mg q2w regimen (1.8%) at Week 52. A lower proportion of patients at the 300 mg q2w-q4w regimen (86%) maintained steady-state trough concentrations above the EC50 (1.75 mg/L) of NPS response compared to 300 mg q2w (97%) (see below). The proportion of patients who maintained Week 52 steady-state trough concentrations above the EC90 (15.8 mg/L) of NPS response was 98%, and 41% at 300 mg q2w and 300 mg q2w-q4w regimens, respectively.

Based on these observations, complete saturation of target mediated elimination may not have been maintained in all patients in the 300 mg q2w-q4w regimen after switching to a 300 mg q4w schedule and we cannot exclude disease control erosion with 300 mg q4w regimen upon longer term dosing eg, after 52-week treatment period.

C) Pharmacokinetic Results (study ACT2340)

Following SC administration of dupilumab at 300 mg qw following a 600 mg loading dose on Day 1, trough concentrations (C_{trough}) increased with each subsequent dose administration, and appeared to reach steady state by Week 12 with mean (SD) steady-state C_{trough} of 166.4 (52.8) mg/L. Accumulation, as assessed by C_{trough} following the 12th dose relative to that after the 1st dose, was 2.18-fold.

Figure 14 Plot of serum concentration (NG/ML) of SAR231893 at each visit



Immunogenicity Results:

A low incidence of treatment-emergent ADA response was observed in both treatment groups. Treatment-emergent ADAs were reported in 3 out of 30 patients who received dupilumab treatment and 4 out of 30 patients who received placebo. The PK exposure in ADA positive patients was within the variability of that in ADA negative patients. No definitive conclusion could be made on the impact of ADA on PK given the small sample size and limited incidence of treatment-emergent ADA in ACT12340.

Pooled immunogenicity Results

Given the different measurement time points and limited patient numbers in Study ACT12340, a summary of ADA, and NAb incidence for CRSwNP patients is provided and pooled only for Studies EFC14146 and EFC14280.

Table 9 ADA incidence in Phase 3 studies in patients with CRSwNP (Studies EFC14146 and EFC14280)

Anti-dupilumab antibodies N (%)	Pooled (24-week duration)[h]		Study EFC14280 (52-week TEAE period)[h]			Study EFC14146 (24-week TEAE period)[h]	
	Placebo (N=281)	300 mg q2w (N=438)	Placebo (N=149)	300 mg q2w–q4w (N=148)	300 mg q2w (N=148)	Placebo (N=132)	300 mg q2w (N=143)
Pre-existing ADA[a]	6 (2.1%)	9 (2.1%)	4 (2.7%)	4 (2.7%)	4 (2.7%)	2 (1.5%)	1 (0.7%)
Treatment-emergent response[b]	6 (2.1%)	19 (4.3%)	6 (4.0%)	12 (8.1%)	8 (5.4%)	7 (5.3%)	22 (15.4%)
Persistent response[c]	2 (0.7%)	7 (1.6%)	1 (0.7%)	5 (3.4%)	3 (2.0%)	2 (1.5%)	5 (3.5%)
Indeterminate response[d]	2 (0.7%)	5 (1.1%)	2 (1.3%)	4 (2.7%)	2 (1.4%)	1 (0.8%)	8 (5.6%)
Transient response[e]	2 (0.7%)	7 (1.6%)	3 (2.0%)	3 (2.0%)	3 (2.0%)	4 (3.0%)	9 (6.3%)
Peak post-baseline titer							
Low (<1,000)	5 (1.8%)	15 (3.4%)	4 (2.7%)	11 (7.4%)[i]	6 (4.1%)	7 (5.3%)	20 (14.0%)
Moderate (1,000-10,000)	1 (0.4%)	0	2 (1.3%)	0	0	0	1 (0.7%)
High (>10,000)	0	4 (0.9%)[g]	0	1 (0.7%)	2 (1.4%)	0	1 (0.7%)[g]
Treatment-boosted response[f]	1 (0.4%)	0	1 (0.7%)	0	0	0	0
Neutralizing antibodies	2 (0.7%)	11 (2.5%)	3 (2.0%)	9 (6.1%)	5 (3.4%)	0	15 (10.5%)

a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.

b A positive response in the ADA assay post first dose when baseline results are negative or missing.

c Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.

d Treatment-emergent response with only the last collected sample positive in the ADA assay.

e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.

f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

g Includes one patient with high titer ADA in the placebo group who was administered one dose of dupilumab

h Includes 24 weeks follow-up for Study EFC14146 and limited number patients with 12 weeks follow-up for Study EFC14280) and the no follow-up period Pooled 24-week treatment pool

i Includes one patient with low titer ADA in the placebo group who was administered one dose of dupilumab

The pool of dupilumab 300 mg q2w arms in Studies EFC14146 and EFC14280 is the principal source of data to evaluate ADA responses in patients with CRSwNP with the same treatment duration (24 weeks) and enables an adequate evaluation of ADA responses. The incidence of treatment-emergent ADA was 4.3% in the 300 mg q2w group compared to 2.1% in the placebo group. Persistent ADA response was observed in 1.6% of all patients at 300 mg q2w compared to 0.7% for placebo. Most of these treatment emergent ADA responses were low titer. High titer ADA response (>10 000) was observed in 0.9% of patients treated with dupilumab and was not observed in patients on placebo. Approximately 2.5% of all patients at 300 mg q2w were classified as neutralizing antibody (NAb) positive compared to 0.7% in the placebo group.

The treatment-emergent ADA incidence was similar (2.1 to 4.8%) following dupilumab treatment for 24 weeks (300 mg q2w in Study EFC14146) or 52 weeks (300 mg q2w and 300 mg q2−q4w in Study EFC14280) as well as placebo treatment (0.7% to 4.8% in Studies EFC14146 and EFC14280). However, the proportion of patients with a treatment-emergent ADA positive response in the post-treatment period varied depending on the follow-up duration (13.7% for 300 mg q2w with 24-week follow-up in Study EFC14146 versus 2.4% for 12-week follow-up in Study EFC14280) and dose regimen (14.3% for 300 mg q2w-q4w versus 2.4% for 300 mg q2w in Study EFC14280). It is to be noted that the 24-week treatment pool does not include a follow-up period, while a 12 to 24-week follow-up duration is included in the TEAE period for Studies EFC14146 and EFC14280, which explains the apparent numerical difference of treatment-emergent ADA incidence between the pool and the individual studies

Table 10 ADA incidence in patients with CRSwNP, asthma and AD in 52-week studies (EFC14280, EFC13579 and AD-1224)

Anti-dupilumab antibodies N (%)	Study EFC14280 (CRSwNP)		Study EFC13579 (Asthma)		Study AD-1224 (AD)		Combined CRSwNP, asthma and AD	
	Placebo (N=149)	300 mg q2w (N=148)	Placebo[g] (N=630)	300 mg q2w (N=626)	Placebo (N=305)	300 mg q2w (N=105)	All Placebo[h] (N=1084)	300 mg q2w (N=879)
Pre-existing ADA[a]	4 (2.7%)	4 (2.7%)	7 (1.1%)	9 (1.4%)	18 (5.9%)	3 (2.9%)	29 (2.7%)	16 (1.8%)
Treatment-emergent response[b]	6 (4.0%)	8 (5.4%)	22 (3.5%)	32 (5.1%)	20 (6.6%)	6 (5.7%)	48 (4.4%)	46 (5.2%)
Persistent response[c]	1 (0.7%)	3 (2.0%)	7 (1.1%)	13 (2.1%)	9 (3.0%)	2 (1.9%)	17 (1.6%)	18 (2.0%)
Indeterminate response[d]	2 (1.3%)	2 (1.4%)	13 (2.1%)	9 (1.4%)	7 (2.3%)	2 (1.9%)	22 (1.8%)	13 (1.5%)
Transient response[e]	3 (2.0%)	3 (2.0%)	2 (0.3%)	10 (1.6%)	4 (1.3%)	2 (1.9%)	9 (0.8%)	15 (1.7%)
High Titer	0	2 (1.4%)	1 (0.2%)	3 (0.5%)	0	0	1 (0.1%)	5 (0.6%)
Treatment-boosted response[f]	1 (0.7%)	0	3 (0.5%)	1 (0.2%)	1 (0.3%)	1 (1.0%)	5 (0.5%)	2 (0.2%)
Neutralizing antibodies	3 (2.0%)	5 (3.4%)	10 (1.6%)	14 (2.2%)	2 (0.7%)	1 (1.0%)	15 (1.4%)	20 (2.3%)

a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.

b A positive response in the ADA assay post first dose when baseline results are negative or missing.

c Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.

d Treatment-emergent response with only the last collected sample positive in the ADA assay.

e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.

f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

g Combined ADA data from placebo 1.14 mL and placebo 2 mL treatments in Study EFC13579

h Includes combined ADA data from placebo 1.14 mL and placebo 2 mL treatments in Study EFC13579

5.4% of patients with CRSwNP who received dupilumab 300 mg q2w for 52 weeks developed antibodies to dupilumab. 2.0% of patients exhibited persistent ADA responses, and 3.4% had neutralizing antibodies while 4.0% of patients in the placebo group in the 52-week study were positive for antibodies to dupilumab. A total of 0.7% of patients exhibited persistent ADA response and 2.0% had neutralizing antibodies. The ADA incidence was similar across the CRSwNP, AD, and asthma populations with respect to treatment emergent positive ADA response (5-6%), persistent ADA response (~2%), and neutralizing antibody response (1-3%) after 52 weeks of treatment at 300 mg q2w.

Although treatment-emergent ADA positive patients appeared to have lower mean exposure compared with that of ADA negative patients, the individual exposures observed in patients with low to moderate titer ADA response were generally within the exposure range in ADA negative patients. Reduced dupilumab exposures were observed in very few patients with high titer ADA responses (N=3 with dupilumab concentration data including one patient who discontinued treatment at Week 20), with dupilumab concentrations that decreased from Week 4 onward and then stayed below or close to LLOQ of the assay (0.078 mg/L). In patients who developed ADA (including NAb) response with low to moderate titer no clear evidence was seen of lack or loss of efficacy. Two of the 3 patients who had high titer ADAs and low drug concentration had an apparent lack of treatment effect. The safety profile in patients with a positive ADA status appeared similar to that of patients with a negative ADA status.

Absorption

In patients with CRSwNP, dupilumab is well-absorbed. A model-estimated SC bioavailability of 62.8% has been reported. This is similar to the reported bioavailability of 64% in the adult AD patient population of the initial AD submission.

Based on the CRSwNP Pop PK model, the median time to steady-state was 16 weeks for 300 mg q2w without a loading dose in a typical individual. When switched from 300 mg q2w to 300 mg q4w at Week 24, the model predicted that a new steady state was achieved after an additional 24 weeks (ie, 48 weeks from the start of dupilumab treatment) (see also POP PK MODEL BASED SIMULATION in Section 3.3.4 of this AR).

The observed trough concentrations and Pop PK model-based post hoc estimates of dupilumab exposure at steady state (Ctrough) are summarized below for CRSwNP Phase 2 and 3 studies.

Table 13 - Descriptive statistics (mean (SD) [%CV]) for model-derived steady state PK exposures in NP patients by study and treatment

Study	Phase	Dose Regimen	Time	Predicted				Observed[f]	
				N	$AUC_{\tau,ss}$ (mg · day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	N	$C_{min,ss}$ (mg/L)
ACT12340	2	300 mg qw[a]	week 15-16	28	1210 (360) [29.8%][c]	177 (52.2) [29.5%]	165 (49.9) [30.3%]	29	176 (52.4)
EFC14146	3	300 mg q2w	week 22-24	135	1100 (424) [38.5%][d]	86.5 (31.5) [36.4%]	65.4 (28.0) [42.9%]	136	69.2 (36.9)
EFC14280	3	300 mg q2w	week 22-24	285	1251 (464) [37.1%][d]	97.6 (34.3) [35.2%]	75.9 (30.8) [40.6%]	--	--
		300 mg q2w	week 50-52	135	1307 (472) [36.1%][e]	102 (35.1) [34.4%]	79.3 (31.4) [39.6%]	95	75.5 (33.5)
		300 mg q2w-q4w[b]	week 48-52	141	929 (483) [52.0%][e]	46.5 (19.6) [42.2%]	17.9 (13.7) [76.5%]	103	17.6 (17.4)

Abbreviation: $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to τ at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; CV: coeffiecient of variation; N: subject number after excuding the discontinued patients; qw: every week; q2w: every two weeks; q4w: every four weeks.

a. Dosing regimen for study ACT12340 is 300mg qw with a loading dose of 600 mg.

b. In study EFC14280, one treatment arm is 300 mg q2w-q4w, which represents 300 mg q2w until Week 24, then 300 mg q4w until Week 52.

c. $AUC_{\tau,ss}$ = AUC[week 15 – week 16] for 300 mg qw (with a loading dose of 600 mg) from study ACT12340; Two discontinued patients out of 30 patients (before week 15) in study ACT12340 were excluded in this statistical summary table.

d. $AUC_{\tau,ss}$ = AUC[week 22 – week 24] for 300 mg q2w from Studies from Studies EFC14146 and EFC14280; Six discontinued patients out of 141 patients (before week 22) in study EFC14146 and 9 discontinued patients out of 294 patients (before week 22) in study EFC14280 were excluded in this statistical summary table.

e. $AUC_{\tau,ss}$ = AUC[week 50 – week 52] for 300 mg q2w and AUC[week 48 – week 52] for 300 mg q4w from study EFC14280. Thirteen discontinued patients out of 148 patients (before week 50) in 300 mg q2w arm and 5 discontinued patients out of 146 (before week 48) in 300 mg q4w of study EFC14280 were excluded in this statistical summary table.

f. Observed $C_{min,ss}$ was from the clinical study reports of studies ACT12340, EFC14146 and EFC14280.

Distribution

Distribution primarily took place within the vascular compartment (model-estimated volume of distribution at 4.91 L). For monoclonal antibodies, limited volume of distribution is expected.

Elimination

For a monoclonal antibody, the elimination of dupilumab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids, and therefore, no specific metabolism or excretion studies were conducted.

Dupilumab exhibits saturable target-mediated elimination. At the PK steady-state concentration for the 300 mg q2w regimen, the PK data show a small deviation from dose-proportional increases in exposure. After the last SC dose at steady state, the model-predicted median time for dupilumab concentration to decline from PK steady state to below the LLOQ (0.078 mg/L) level was 12 weeks for the 300 mg q2w and 6 weeks for the 300 mg q2w−q4w regimen. These parameters are consistent with those reported for dupilumab in the AD and asthma population.

Linear clearance has been derived to 0.113 L/day, which is comparable to the CL in the asthma (0.115) and AD population (0.131).

Dose proportionality and time dependencies

- Dose proportionality

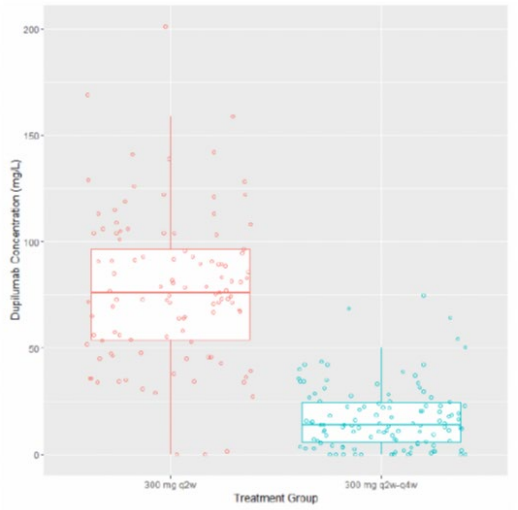
Monoclonal antibodies characterized by nonlinear target-mediated kinetics, such as dupilumab, are found to exhibit a greater than dose-proportional increase in exposure. This nonlinear PK profile is typically observed at drug concentrations below that required to saturate the target-mediated clearance pathway. As drug concentrations increase to levels greater than those required to saturate the target-mediated pathway, the PK profile reverts to a dose-proportional profile.

Cross study comparison of observed Ctrough (Studies ACT12340, EFC14146, and EFC14280), showed 2.37−2.75-fold increase from 64.0−74.4 mg/L to 176 mg/L in the mean Ctrough at Week 16 for a 2-fold dose increase from 300 mg q2w to 300 mg qw. In Study EFC14280, there was a 4.29-fold increase from 17.6 mg/L to 75.5 mg/L in the mean Ctrough at Week 52 for a 2-fold dose increase from 300 mg q4w to 300 mg q2w. Although there are limitations in comparison of Ctrough for different dosing regimens, the results were consistent with $AUC_{T,ss}$, suggesting a greater than dose proportional increase between 300 mg q4w and 300 mg q2w and then a close to dose proportional increase between 300 mg q2w to 300 mg qw.

Based on the CRSwNP Pop PK model-based post hoc estimates, cross study comparison of $AUC_{T,ss}$ at steady state, mean $AUC_{T,ss}$ were similar for 300 mg q2w to 300 mg qw, indicating no major deviation from dose proportionality between 300 mg q2w to 300 mg qw and suggesting a saturation of the target-mediated elimination at doses of 300 mg q2w and higher.

A greater than dose proportional increase in exposure from 300 mg q4w to 300 mg q2w suggests that some patients may have not reached full saturation of the target-mediated elimination at the steady-state exposure of 300 mg q4w. More patients in the 300 mg q2w−q4w regimen (8.7%) had steady-state Ctrough at the end of the 52-week treatment that were below the limit of quantitation (0.078 mg/L) than those in the 300 mg q2w regimen (1.8%).

Figure 7 - Box plot of dupilumab trough concentrations at Week 52 in individual patients with CRSwNP at 300 mg q2w and 300 mg q2w–q4w (Study EFC14280)



The boxplot has individual observed data (as open circles). Lower and upper end of whisker indicate 5th and 95th percentile of C_{trough}; lower and upper boundary of the box and the median line represent the 25%, 75% and 50% percentiles of C_{trough}.
Source document: 5.3.3.5 Study POH0611 report of CRSwNP Pop PK analysis.

Mean (SD) steady-state exposure of dupilumab in patients with CRSwNP (Studies ACT12340, EFC14146, and EFC14280)

Study identifier	Dose		$C_{max,ss}$ (mg/L)	$AUC_{\tau,ss}$ (mg•day/L)		$C_{trough,ss}$ (mg/L)	
		N	Predicted[b]	Predicted[b]	Predicted[b]	N	Observed
ACT12340[a]	300 mg qw	28	177 (52.2)	1210 (360)	165 (49.9)	29	176 (52.4)
EFC14146	300 mg q2w	135	86.5 (31.5)	1100 (424)	65.4 (28.0)	136	69.2 (36.9)
EFC14280	300 mg q2w	135	102 (35.1)	1307 (472)	79.3 (31.4)	95	75.5 (33.5)
	300 mg q2w–q4w	141	46.5 (19.6)	929 (483)	17.9 (13.7)	103	17.6 (17.4)

Abbreviation: N: number of patients; $AUC_{\tau,ss}$: Area under the concentration time curve over the dosing interval (τ) at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; qw: once every week; q2w: every two weeks; q4w: every four weeks; NA: not applicable; SD: standard deviation

a Dose regimen of 300 mg qw with a loading dose of 600 mg in ACT12340

b Predicted: summary statistics of post hoc estimates of exposure parameters based on the CRSwNP Pop PK model in Study POH0611

$AUC_{\tau,SS}$ = AUC[Week 15 – Week 16] for 300 mg qw from Study ACT12340

$AUC_{\tau,SS}$ = AUC[Week 22 – Week 24] for 300 mg q2w from Study EFC14146

$AUC_{\tau,SS}$ = AUC[Week 50 – Week 52] and AUC[Week 48 – Week 52] for 300 mg q2w and 300 mg q4w from Studies EFC14280

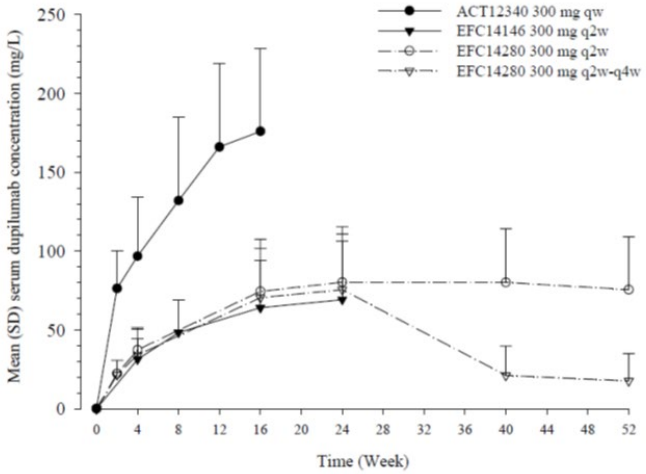
$C_{trough,ss}$ represents the mean trough concentration at Week 16 for Study ACT12340, and Week 24 for Study EFC14146, Week 52 for Study EFC14280

- Time dependency

Following the administration of a 600 mg loading dose for the 300 mg qw regimen to patients with CRSwNP in the Phase 2a Study ACT12340, dupilumab concentrations rose to a mean value of 76.3 mg/L at Week 2. The concentrations continued to increase over time and reached a mean steady state (Ctrough) level of 166 mg/L by Week 12 (Figure 5). In the pivotal Phase 3 studies (EFC14146 and EFC14280), without a loading dose, 300 mg q2w resulted in a mean dupilumab trough concentration of 21.5–22.3 mg/L at Week 2 and a mean steady-state trough level of 69.2–80.2 mg/mL at Week 24. The steady state Ctrough was achieved by Week 16 and was maintained up to

52 weeks for the q2w regimen during treatment in patients with CRSwNP. These results indicate the lack of a time-dependent change in dupilumab PK.

Figure 5 - Mean (SD) observed trough concentration-time profiles of dupilumab at 300 mg qw (with loading dose) in a Phase 2 study and at 300 mg q2w and 300 q2w–q4w (without loading dose) in Phase 3 studies in patients with CRSwNP



Note: The mean concentration-time profiles are presented to the end of treatment in each study.
Sources: Studies ACT12340, EFC14146 and EFC14280 PK appendices, see 5.3.5.1 Studies ACT12340, EFC14146 and EFC14280, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.1.1].

Special populations

Sources of pharmacokinetic variability

In the pivotal studies in the CRSwNP population the observed variability of steady state trough concentrations after repeated SC doses of dupilumab 300 mg q2w was in the range of 42.6 to 53.4%. For the 300 mg q2w–q4w group (Study EFC14280) the observed variability of steady state trough concentrations was in the range of 88.3 to 98.4% following the decrease in dose to 300 mg q4w. Consistently the CRSwNP Pop PK analysis showed moderate IIV in PK parameters Fsc(41.9%), Ka(44.0%), Ke(17.2%), V2(8.09%), and Vmax (29.1%) (Study POH0611).

Overview of the subjects' characteristics in the final pop PK data set

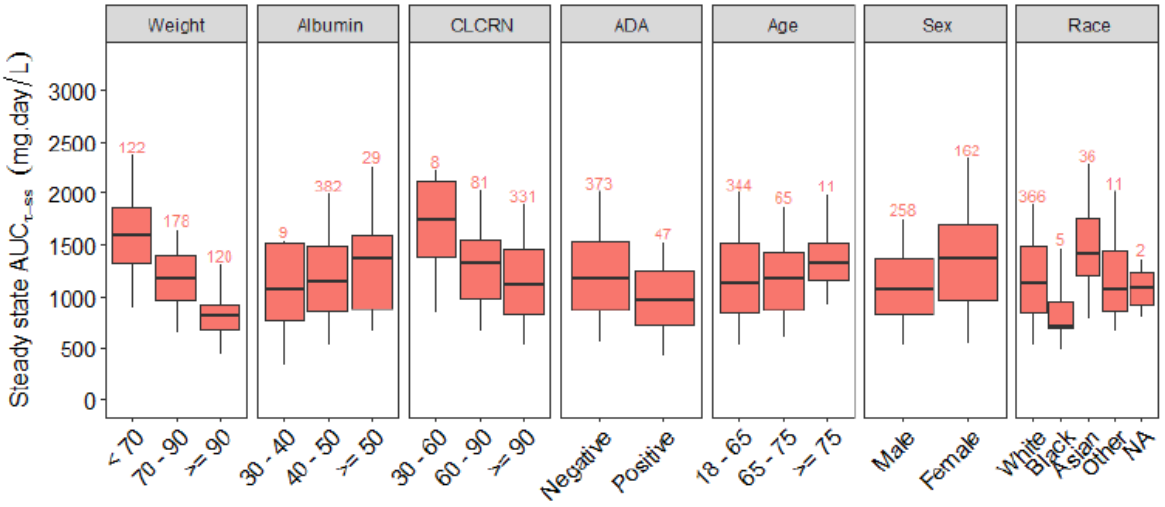
Covariate candidates	ACT12340			EFC14146			EFC14280			Total		
	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)
Weight (kg)	30	84.5 (16.6)	83.0 (55.2 – 126)	141	81.6 (18.0)	79.4 (38.0 – 130)	294	79.7 (17.9)	78.8 (39.4 – 150)	465	80.6 (17.9)	79.0 (38.0 – 150)
Age (Year)	30	48.0 (9.84)	48.7 (25.6 – 63.1)	141	50.8 (13.7)	52.4 (23.2 – 79.7)	294	52.7 (12.3)	52.3 (19.1 – 83.3)	465	51.8 (12.7)	52.0 (19.1 – 83.3)
CLCR (mL/min)	29[a]	119 (34.0)	109 (65.3 – 189)	141	124 (36.3)	116 (56.1 – 233)	294	128 (45.7)	121 (35.9 – 329)	464	127 (42.3)	120 (35.9 – 329)
CLCRN (mL/min/1.73 m2)	29[a]	103 (24.2)	97.2 (66.8 – 153)	141	110 (26.3)	108 (60.7 – 182)	294	116 (34.9)	110 (34.3 – 303)	464	114 (32.1)	109 (34.3 – 303)
Albumin (g/L)	30	42.7 (2.40)	42.0 (38.0 – 47.0)	141	46.1 (2.81)	46.0 (39.0 – 54.0)	294	45.0 (2.87)	45.0 (37.0 – 53.0)	465	45.2 (2.93)	45.0 (37.0 – 54.0)
EoS (cells/mm3)	30	406 (236)	355 (110 – 1190)	141	425 (313)	340 (0 – 2110)	294	423 (349)	330 (20.0 – 2900)	465	422 (332)	340 (0 – 2900)
NPS	30	5.87 (1.01)	6.0 (3.0 – 8.0)	141	5.65 (1.24)	5.50 (2.0 – 8.0)	294	6.18 (1.21)	6.0 (1.5 – 8.0)	465	6.00 (1.23)	6.00 (1.50 – 8.00)
NC	30	1.66 (0.73)	1.57 (0.6 – 3.0)	141	2.26 (0.58)	2.0 (1.0 – 3.0)	294	2.47 (0.59)	2.71 (0 – 3.0)	465	2.35 (0.63)	2.29 (0– 3.00)

Abbreviation: CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by BSA; EoS: eosinophil; NC:nasal congestion; NPS:nasal polyp score. N: subject number; SD: standard deviation.
a.One patient from study ACT12340 with missing information for CLCR and CLCRN was excluded from the summary. In the Pop PK analysis, the missing CLCR and CLCRN values for this patient were imputed using population median of CLCR and CLCRN.

Covariate candidates	Subgroup	Act12340 N (%)	EFC14146 N (%)	EFC14280 N (%)	Total N (%)
Gender	Male	18 (60%)	87 (61.7%)	183 (62.2%)	288 (61.9%)
	Female	12 (40%)	54 (38.3%)	111 (37.8%)	177 (38.0%)
Race[a]	Caucasian	29 (96.7%)	136 (96.4%)	243 (82.7%)	408 (87.7%)
	Black	1 (3.3%)	2 (1.4%)	4 (1.4%)	7 (1.5%)
	Asian	0 (0%)	1 (0.7%)	36 (12.2%)	37 (8.0%)
	Other	0 (0%)	1 (0.7%)	10 (3.4%)	11 (2.4%)
	Missing	0 (0%)	1 (0.7%)	1 (0.3%)	2 (0.4%)
Stationary ADA	Negative	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Pre-existing	7 (23.3%)	1 (0.7%)	8 (2.7%)	16 (3.4%)
	Treatment-emergent	3 (10%)	3 (2.1%)	12 (4.1%)	18 (3.9%)
	Treatment-boosted	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stationary ADA	Non-positive	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Positive	10 (33.3%)	4 (2.8%)	20 (6.8%)	34 (7.3%)
Stationary ADA	Negative ADA	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	0< titers <1000	7 (23.3%)	4 (2.8%)	17 (5.8%)	28 (6.0%)
	1000<= titers <=10000	3 (10%)	0 (0%)	0 (0%)	3 (0.6%)
	titers >10000	0 (0%)	0 (0%)	3 (1.0%)	3 (0.6%)
UPSIT[b]	Normal loss of smell	0 (0%)	4 (2.8%)	5 (1.7%)	9 (1.9%)
	Mild hyposmia	0 (0%)	8 (5.7%)	11 (3.7%)	19 (4.1%)
	Moderate hyposmia	0 (0%)	9 (6.4%)	15 (5.1%)	24 (5.2%)
	Severe hyposmia	0 (0%)	15 (10.6%)	28 (9.5%)	43 (9.2%)
	Anosmia	30 (100%)	100 (70.9%)	218 (74.1%)	348 (74.8%)
	Missing	0 (0%)	5 (3.5%)	17 (5.8%)	22 (4.7%)
ASTH	With	16 (53.3%)	80 (56.7%)	176 (59.9%)	272 (58.5%)
	Without	14 (46.7%)	61 (43.3%)	118 (40.1%)	193 (41.5%)
INCS	Once a day	2 (6.7%)	10 (7.1%)	58 (19.7%)	70 (15.1%)
	Twice a day	28 (93.3%)	131 (92.9%)	236 (80.3%)	395 (85.0%)
ANTIH	With	4 (13.3%)	11 (7.8%)	49 (16.7%)	64 (13.8%)
	Without	26 (86.7%)	130 (92.2%)	245 (83.3%)	401 (86.2%)
OCS	With	1 (3.3%)	87 (61.7%)	225 (76.5%)	313 (67.3%)
	Without	29 (96.7%)	54 (38.3%)	69 (23.5%)	152 (32.7%)
ALLE	With	0 (0%)	2 (1.4%)	8 (2.7%)	10 (2.15%)
	Without	30 (100%)	139 (98.6%)	286 (97.3%)	455 (97.85%)

Abbreviation: ADA: anti-drug antibody; ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; ASTH: patients with comorbid asthma; INCS: intranasal corticosteroid spray; OCS: oral corticosteroids; UPSIT: university of Pennsylvania smell identification test.
a. Two patients from studies EFC14146 and EFC14280 had missing information for race. In Pop PK analysis, the missing race values those patients were imputed using the categorical value of the majority population.
b. Five patients from study EFC14146 and 17 patients form EFC14280 had missing information for UPSIT. In Pop PK analysis, the missing UPSIT values for those patients were imputed using the categorical value of the majority population.

Dupilumab steady-state exposure (AUCτ,ss) by covariate category in patients with CRSwNP from Studies EFC14146 and EFC14280 (Study POH0611) by demographic, laboratory parameter, and ADA covariate category



- Body weight

Body weight was determined to be the key factor contributing to PK variability in patients with AD and asthma. Similarly, body weight was the primary source of dupilumab PK variability in patients with CRSwNP.

The range in body weight in the CRSwNP Pop PK population was 38 to 150 kg, with a significant effect on linear elimination rate constant (Ke), central compartment volume (V2) and maximum rate of target mediated elimination (Vmax) (Study POH0611).

The greater effect of body weight on steady state exposure at 300 mg q4w than at 300 mg q2w is consistent with the greater IIV at 300 mg q4w. These data suggest that the steady state exposure at 300 mg q2w−q4w is more sensitive to the effect of weight compared to 300 mg q2w, which is likely due to non-linear saturable target-mediated elimination predominating at lower concentrations towards the end of the 300 mg q4w dosing interval.

Mean (SD) dupilumab steady-state exposure by body weight category in patients with CRSwNP (Study POH0611)

	300 mg q2w				300 mg q2–q4w			
Body weight (kg)	**N**	**$AUC_{\tau,ss}$[a] (mg•day/L)**	**$C_{max,ss}$ (mg/L)**	**$C_{trough,ss}$ (mg/L)**	**N**	**$AUC_{\tau,ss}$[a] (mg•day/L)**	**$C_{max,ss}$ (mg/L)**	**$C_{trough,ss}$ (mg/L)**
<70 kg	122	1618 (431)	125 (31.6)	99.6 (28.9)	45	1286 (480)	61.5 (19.1)	27.6 (14.2)
70 to < 90 kg	178	1170 (328)	91.7 (23.9)	70.3 (22.2)	57	934 (367)	46.6 (14.4)	17.9 (10.7)
≥90 kg	120	827 (256)	65.7 (18.8)	48.3 (17.3)	39	511 (256)	29.0 (10.3)	6.73 (7.06)

a $AUC_{\tau,ss} = AUC_{[Week\ 22 - Week\ 24]}$ for 300 mg q2w.

Descriptive statistics represent the post hoc estimates of steady-state exposure for Studies EFC14146 and EFC14280, Study POH0611 NP Pop PK analysis report, see 5.3.3.5 Study POH0611

There was no clinically meaningful difference in dupilumab efficacy or safety profiles across the weight categories in patients with CRSwNP.

- Age

The CRSwNP Pop PK analysis (Study POH0611) with data from CRSwNP patients ranging in age from 19.1 to 83.3 years did not identify age as a significant covariate influencing dupilumab PK.

It should be noted that there was a very limited number of patients ≥75 years (N=11), representing 2.4% of total patients in the Pop PK dataset. However, 81 patients ≥65 years of age, representing 17.4% of total patients are included in the Pop PK dataset.

A summary of post hoc estimates of individual steady-state exposure for patients in the pivotal Phase 3 studies (EFC14146 and EFC14280) is presented by age category in Table 9. The differences in dupilumab exposure across the age categories were not considered to be clinically meaningful and, therefore, a dose adjustment for age is not recommended in patients with CRSwNP.

The pharmacokinetics of dupilumab in paediatric patients (<18 years of age) with CRSwNP has not been studied.

Table 9 - Mean (SD) dupilumab steady-state exposure by age category in patients with CRSwNP in Studies EFC14146 and EFC14280 (Study POH0611)

	300 mg q2w			
Age (year)	N (median weight)	$AUC_{\tau,SS}$[a] (mg•day/L)	$C_{max,SS}$ (mg/L)	$C_{trough,SS}$ (mg/L)
≥18 - <65	344 (80.0 kg)	1201 (465)	93.8 (34.5)	72.5 (30.7)
≥65 - <75	65 (73.0 kg)	1181 (423)	92.8 (31.1)	70.9 (28.6)
≥75	11 (70.0 kg)	1377 (369)	107 (26.6)	84.9 (26.0)

a $AUC_{\tau,SS}$ = AUC[week 22 – week 24] for 300 mg q2w

Descriptive statistics represent the post hoc estimates of steady-state exposure for Studies EFC14146 and EFC14280, Study POH0611 NP Pop PK analysis report, see 5.3.3.5 Study POH0611

- Gender

No difference has been seen in the observed dupilumab concentrations between female and male patients in CRSwNP studies (EFC14146 and EFC14280). Similar to the previous finding for AD patients and asthma patients, the CRSwNP Pop PK analysis (Study POH0611) of data from 288 male and 177 female subjects did not identify gender as a significant covariate for dupilumab PK. Consistently, there is no notable difference in post hoc estimates of individual steady-state exposure between male and female CRSwNP patients.

- Race/ethnicity

Race was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab by population PK analysis.

The CRSwNP Pop PK analysis (Study POH0611) of the data consisting of Caucasian (N=408, 87.7%), Asian (N=37, 8.0%; includes Asian patients from all counties), Black (N=7, 1.5%), and other patients (N=11, 2.4%) did not identify race as a significant covariate impacting dupilumab pharmacokinetics.

A trend of higher exposure in Asians compared to Caucasians in the observed concentrations and the post hoc estimates of individual steady-state exposure was seen. This effect is primarily explained by the difference in body weight (median body weight of 64.6 kg in Asians versus 80.0 kg in Caucasians). Similarly, the higher mean exposure in this subset of Japanese patients versus the rest of the population (non-Japanese) is mainly the result of differences in body weight.

- Renal impairment

Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of dupilumab. Very limited data are available in patients with severe renal impairment.

In the CRSwNP Pop PK analysis population (Study POH0611), the majority of subjects had normal renal function (N=383, 82.5%) or mild renal impairment (N=71, 15.3%). A small number of subjects had moderate renal impairment (N=10, 2.2%) and none had severe renal impairment. Creatinine clearance did not have a statistically significant effect on dupilumab PK in the CRSwNP population. Consistently, there was considerable overlap in individual steady-state exposure between patients with mild or moderate renal impairment and normal renal function (Table 10). The apparent difference in mean exposures between categories from this post hoc univariate analysis is due to the confounding effect of body weight and is not a reflection of a direct effect of renal function on dupilumab PK. Therefore, a dose adjustment for renal function is not considered necessary.

Table 10 - Mean (SD) dupilumab steady-state exposure by renal function category in patients with CRSwNP in Studies EFC14146 and EFC14280 (Study POH0611)

CLCR (mL/min)	300 mg q2w			
	N (median weight)	$AUC_{\tau,SS}$[a] (mg•day/L)	$C_{max,SS}$ (mg/L)	$C_{trough,SS}$ (mg/L)
≥ 30 - < 60	9 (67.0 kg)	1633 (511)	126. (37.3)	102 (34.8)
≥ 60 - < 90	62 (65.0 kg)	1544 (466)	119 (34.3)	94.9 (31.3)
≥ 90	349 (82.0 kg)	1130 (419)	88.7 (31.1)	67.8 (27.8)

a $AUC_{\tau,SS}$ = AUC[week 22 – week 24] for 300 mg q2w

Descriptive statistics represent the post hoc estimates of steady-state exposure for Studies EFC14146 and EFC14280, Study POH0611 NP Pop PK analysis report, see 5.3.3.5 Study POH0611

- Hepatic function

Antibodies, such as dupilumab, are not cleared through the liver and instead are eliminated primarily via proteolytic catabolism by the reticulo-endothelial system distributed throughout the body. As such, no formal study was conducted to assess the effect of hepatic impairment on dupilumab PK.

- Albumin

Albumin did not have a statistically significant effect on dupilumab PK in the CRSwNP population (Study POH0611). In the previous AD and asthma Pop PK analyses, albumin had a statistically significant, but not clinically meaningful, effect on dupilumab PK.

Pharmacokinetic interaction

Dupilumab, as a monoclonal antibody, directed against IL-4Rα, is not expected to have a direct or indirect effect on cytochrome P450 (CYP) enzyme-mediated metabolism. This was confirmed in the drug interaction Study R668-AD-1433 in patients with atopic dermatitis, where there was no clinically relevant effect of dupilumab on the activities of CYP isoforms including CYP1A2, 2C9, 2C19, 2D6 and 3A. The results indicate that IL-4/IL-13 has no meaningful impact on CYP enzymes in vivo.

The absence of clinically meaningful modulation of CYP isoforms by dupilumab indicated that clinically relevant drug-drug interactions between dupilumab and CRSwNP agents metabolized by these CYP enzymes are unlikely to occur.

The CRSwNP Pop PK analysis evaluated the effects of 4 classes of common concomitant CRSwNP medications (eg, INCS [QD versus BID], systemic antihistamines, OCS, and allergen immunotherapy) on dupilumab PK. Based on the comparison of post hoc estimates of individual steady-state exposure, the concomitant use of these CRSwNP controller medications has no apparent effect on dupilumab PK (Study POH0611).

Descriptive statistics (mean SD) for post hoc estimates of steady-state exposure of dupilumab in with CRSwNP from Phase 2 and 3 studies by covariates of comorbidities and concomitant medications

Covariate		300 mg q2w (EFC14146 and EFC14280) N	$AUC_{\tau,ss}$[c] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	300 mg qw (ACT12340)[a] N	$AUC_{\tau,ss}$[b] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
All	--	420	1202 (456)	94.0 (33.8)	72.5 (30.3)	28	1210 (360)	177 (52.2)	165 (49.9)
ASTH	With	248	1236 (458)	96.6 (34.0)	74.6 (30.3)	15	1284 (371)	187 (53.9)	175 (51.2)
	Without	172	1154 (451)	90.3 (33.3)	69.5 (30.1)	13	1125 (342)	165 (49.4)	153 (47.4)
ANTIH	With	61	1277 (533)	99.5 (39.5)	77.7 (35.3)	4	1425 (322.6)	208 (46.9)	194 (44.6)
	Without	359	1189 (442)	93.1 (32.7)	71.7 (29.3)	24	1174 (359.9)	172 (52.1)	160 (49.9)
INCS	Once a day	60	1344 (469)	104 (34.8)	81.8 (31.0)	1	1267	186	172
	Twice a day	360	1179 (450)	92.3 (33.4)	71. (29.9)	27	1208 (367)	176 (53.2)	164 (50.8)
ALLE	With	10	1168 (449)	90.9 (33.6)	70.9 (29.5)	28	1210 (360)	177 (52.2)	165 (49.9)
	Without	410	1203 (457)	94.1 (33.8)	72.6 (30.3)	0	--	--	--
OCS	With	311	1202 (448)	93.9 (33.2)	72.6 (29.8)	1	975	143	131
	Without	109	1203 (481)	94.2 (35.6)	72.4 (31.8)	27	1219 (364)	178 (52.8)	166 (50.4)

Abbreviation: ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; ASTH: patients with comorbid asthma; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to τ at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; INCS: intranasal corticosteroid spray; N: number of patients; OCS: oral corticosteroids; qw: once every week; q2w: once every two weeks.

a Dose regimen of 300 mg qw with a loading dose of 600 mg in ACT12340.

b $AUC_{\tau,ss}$ = AUC[week 15 – week 16] for 300 mg qw from Study ACT12340.

c $AUC_{\tau,ss}$ = AUC[week 22 – week 24] for 300 mg q2w from Studies from Study EFC14146 and EFC14280.

No apparent effect of the CRSwNP medication on the PK of Dupilumab has been identified.

2.3.3. Pharmacodynamics

Mechanism of action

Dupilumab is a human monoclonal immunoglobulin-G4 (IgG4) antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling by specifically binding to the IL-4 receptor alpha (IL-4Rα) sub-unit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab inhibits IL-4 signalling via the Type I receptor (IL 4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine- induced responses, including the release of pro-inflammatory cytokines, chemokines, and IgE.

Primary and secondary pharmacology

Blood levels of the type 2 inflammation biomarkers (thymus and activation-regulated chemokine [TARC], total IgE, eosinophil cationic protein [ECP], and periostin) were assessed as markers for disease activity/severity. These same markers and eotaxin-3 were also assessed from nasal secretions to similarly gain an understanding of dupilumab's actions in the sino-nasal cavity. In addition, the dupilumab effect on leukotriene E4 (LTE4) in urine, a stable end product of the cysteinyl leukotriene pathway and a marker of activation of mast cells, involved in type 2 inflammation in patients with CRSwNP and NSAID-ERD, was explored.

a) Study EFC14146

After 24 weeks, markedly decreased concentrations of blood total IgE in the dupilumab group was seen compared to placebo. Moreover, dupilumab treatment reduced levels of urinary LTE4 at Week 24 as compared to placebo. This decrease in LTE4, a type 2 urinary biomarker associated with activation and chemotaxis of mast cells and Th2 cells, was noted both in the dupilumab treated patient population, and in the subgroup of patients with non-steroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

- Serum total IgE

At baseline, serum total IgE concentrations were in the same range among the treatment groups. At week 24 the results show a decline through the treatment period for the dupilumab group of -111.62 IU/mL, while remaining relatively unchanged for the placebo group with +19.06 IU/mL.

Summary of serum total IgE (IU/mL) over time - Safety population

Total IgE	Placebo (N=132)	Dupilumab 300mg q2w (N=143)
Baseline		
Value		
Number	132	143
Mean (SD)	223.45 (269.94)	201.37 (281.50)
Median	122.00	100.00
Q1 : Q3	62.50 : 288.00	49.00 : 217.00
Min : Max	4.0 : 1586.0	3.0 : 1920.0
Week 24		
Value		
Number	130	142
Mean (SD)	245.15 (392.75)	90.36 (132.32)
Median	119.00	45.50
Q1 : Q3	48.00 : 267.00	23.00 : 99.00
Min : Max	5.0 : 3190.0	1.0 : 1115.0
Change from baseline		
Number	130	142
Mean (SD)	19.06 (197.47)	-111.62 (166.18)
Median	-1.00	-54.50
Q1 : Q3	-19.00 : 16.00	-118.00 : -26.00
Min : Max	-229.0 : 1947.0	-843.0 : -2.0
Percentage change from baseline		
Number	130	142
Mean (SD)	4.189 (37.644)	-53.250 (15.107)
Median	-0.546	-54.332
Q1 : Q3	-14.074 : 16.016	-62.658 : -44.444
Min : Max	-96.45 : 236.07	-90.00 : -5.71

- Antigen-specific IgE

There were no notable differences in serum antigen-specific IgE at baseline between the treatment groups. A similar percentage of patients were below the LLOQ for all antigens (31.5% versus 29.5%), greater than or equal to the LLOQ for only one antigen (12.6% versus 14.4%), and greater than or equal to the LLOQ for at least 2 antigens (55.9% versus 56.1%), in the dupilumab and placebo groups respectively.

At week 24, 42.0% of patients in the dupilumab group were below the LLOQ for all antigens compared to 30.3% in the placebo group. A lower percentage of patients in the dupilumab group versus the placebo group were greater than or equal to the LLOQ for at least 2 antigens (43.4% versus 56.8%), regardless of baseline status.

- Plasma eotaxin-3

Due to an error made in the calibration curves established during the quantification of plasma eotaxin-3 and the impact of this error on the accuracy of data the results are not available.

- Urine leukotriene E4

As IL-4/13 upregulates expression of LTE4 synthases in many of the cells involved in type 2 inflammation urinary LTE4 level were assessed. Urinary LTE4 levels are high in patients with nasal polyps, or chronic eosinophilic rhinosinusitis. At baseline, urine LTE4 concentrations were similar among both treatment groups (mean concentration [SD]: 328.35 [650.43] for the dupilumab 300

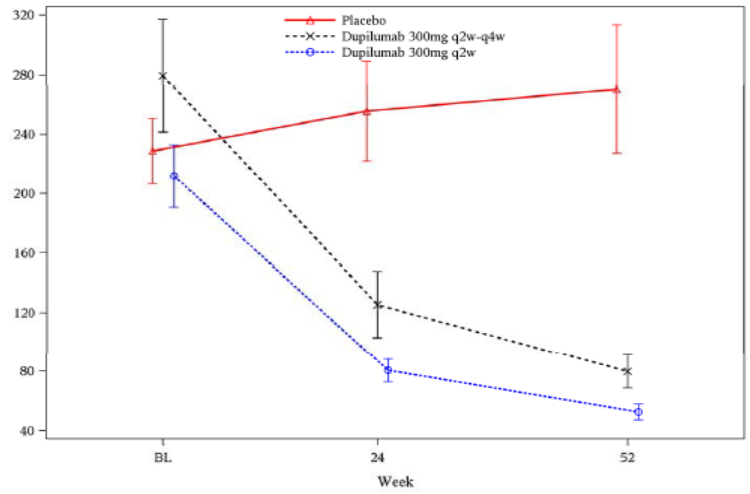
mg q2w and 312.97 [1236.86] for placebo). At Week 24, the mean change in LTE4 from baseline was -234.70 for the dupilumab and -92.19pg/mL for the placebo group, demonstrating a significant higher decrease in urine LTE4 concentration in patients receiving dupilumab. Urine leukotriene E4 in patients with NSAID-ERD history was also assessed. At Week 24, the mean change in LTE4 from baseline was -383.82 and +23.43 pg/mL for the dupilumab 300 mg q2w and the placebo group, respectively. However, the baseline levels were different in this population (mean concentration [SD]: 499.95 [772.80], and 279.30 [412.51] pg/mL for the dupilumab 300 mg q2w and placebo groups, respectively).

b) Study EFC14280

- Serum total IgE

At baseline the serum total IgE concentrations were in the same range among the treatment groups. Throughout the treatment period the concentration of serum total IgE declined in both dupilumab treatment groups, while no decline was seen for placebo. At Week 52, the mean changes from baseline were -156.92 IU/mL for the dupilumab 300 mg q2w group, -189.62 IU/mL for the 300 mg q2w-q4w groups and +64.09 IU/mL for the placebo group. The mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -26.42 IU/mL and -42.67 IU/mL, respectively.

On-treatment analysis: mean (+/-SE) of blood total IgE (IU/ML) over time – Safety population



#subjects			
Placebo	150	144	120
Dupilumab 300mg q2w-q4w	148	146	142
Dupilumab 300mg q2w	148	145	135

Only baseline and on-treatment post-baseline values (from first IMP to end of treatment or last IMP +14 days) are included.

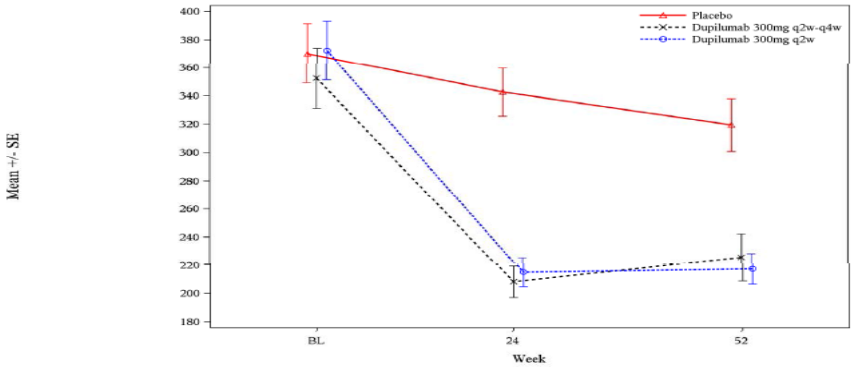
- Serum thymus and activation regulatory chemokine (TARC)/CCL17

At baseline, serum TARC/CCL17 (a type 2 chemokine whose receptor CCR4 is predominantly expressed on Th2 lymphocytes and basophils) concentrations were similar among the treatment groups.

A decrease in TARC was observed at Week 24 and remained at a low level through Week 52 for both dupilumab groups. At Week 52, the mean change in TARC from baseline was -158.53 pg/mL for the dupilumab 300 mg q2w, -126.23 pg/mL for the and 300 mg q2w-q4w groups and -15.09 pg/mL for the placebo group.

The mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was +0.54 pg/ml and +18.00 pg/mL.

On-treatment analysis: mean (+/-SE) of blood TARC (PG/ML) over time – Safety population



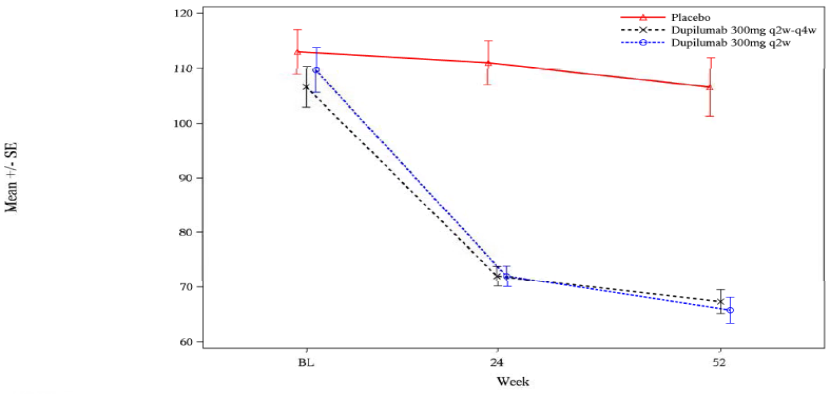
#subjects			
Placebo	149	143	119
Dupilumab 300mg q2w-q4w	148	147	142
Dupilumab 300mg q2w	147	142	134

Only baseline and on-treatment post-baseline values (from first IMP to end of treatment or last IMP +14 days) are included.

- Serum periostin

At baseline, concentrations of serum periostin were similar among the treatment groups. A decrease of periostin was observed at the first assessment at Week 24 and continued through Week 52 for patients in both dupilumab groups (300 mg q2w / dupilumab 300 mg q2w/q4w). At Week 52, the mean change in periostin from baseline was -45.42 ng/mL for the dupilumab 300 mg q2w and -39.79 ng/mL for the 300 mg q2w-q4w groups, while nearly unchanged for the placebo group with -4.73 ng/mL. The mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -6.17 and -4.86 ng/mL, respectively

On-treatment analysis: mean (+/-SE) of blood periostin (NG/ML) over time – Safety population



#subjects			
Placebo	150	142	113
Dupilumab 300mg q2w-q4w	148	147	136
Dupilumab 300mg q2w	147	144	123

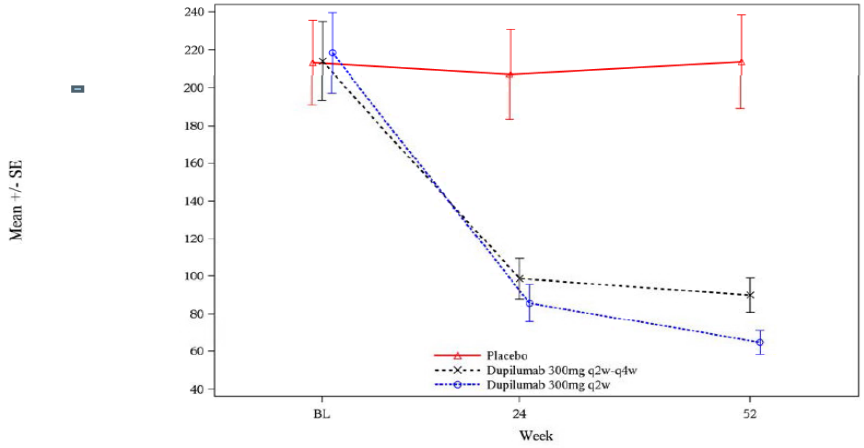
Only baseline and on-treatment post-baseline values (from first IMP to end of treatment or last IMP +14 days) are included.

- Urine leukotriene E4

The urine LTE4 concentrations were similar among the treatment groups at baseline.

A decrease in urine LTE4 was observed at the first assessment at Week 24 and continued to decline to Week 52 for both dupilumab dose groups. At Week 52, the mean change in LTE4 from baseline was -150.48 for the dupilumab 300 mg q2w, -131.10 pg/mL for the dupilumab 300 mg q2w/q4w group and -0.52 pg/mL for the placebo group. So the highest decrease was seen in the 300 mg q2w group.

On-treatment analysis: mean (+/-SE) of spot urine leukotriene E4 (pg/mL) over time -Safety population



#subjects			
Placebo	150	133	117
Dupilumab 300mg q2w-q4w	148	142	139
Dupilumab 300mg q2w	149	137	136

Only baseline and on-treatment post-baseline values (from first IMP to end of treatment or last IMP +14 days) are included.

In patients with NSAID-ERD the mean change in LTE4 from baseline to Week 52was -345.44 for the dupilumab 300 mg q2w, -340.00 pg/mL for the 300 mg q2w-q4w group, and was -14.14 pg/mL for the placebo group.

Sub-study of biomarkers in nasal secretions

In 130 patients a substudy was performed. Nasal secretions were assayed for local biomarkers related to nasosinus inflammation and NP, such as ECP, total IgE, eotaxin-3 at baseline and Week 24. Results presented are not normalized for total proteins in nasal secretions. The analysis of periostin and IL5 in nasal secretion was not available at the time of the database lock for the CSR and will be reported later in a CSR addendum.

ECP and eotaxin-3 concentrations were similar among the treatment groups at baseline. At Week 24, the mean change from baseline in ECP was -31.9 ng/mL for the dupilumab 300 mg q2w and -15.0 ng/mL for the placebo group. The mean change from baseline in eotaxin-3 was -69.471 pg/mL for the dupilumab 300 mg q2w and +24.944 pg/mL for the placebo group. The mean change in from baseline in total IgE was -36.81 IU/mL for the dupilumab 300 mg q2w group and +2.72 IU/mL for the placebo group.

c) Study ACT12340 (supportive study)

Rapid (as early as Week 2) and marked reductions in circulating type 2 biomarkers including TARC and eotaxin-3 concentrations were observed in the dupilumab group compared with placebo. A gradual decrease in blood total IgE was also noted in response to dupilumab treatment. Decreases in type 2 biomarkers from nasal secretions including total IgE, eotaxin-3, ECP and periostin were observed in response to dupilumab treatment, relative to placebo, indicating a direct effect of dupilumab on type 2 inflammation in the nasal tissue.

2.3.4. PK/PD modelling

The effect of intrinsic and extrinsic factors (eg, age, race, gender, disease characteristics, ADA etc.) on dupilumab PK in patients with CRSwNP was evaluated via Pop PK analysis.. In the first Pop PK analysis of dupilumab, conducted using pooled data from the Phase 1 studies in healthy adults and Phase 2 and 3 studies in adult patients with moderate-to-severe AD, body weight was the primary source of dupilumab PK variability. Other identified statistically significant covariates (albumin,

eczema area and severity index [EASI], ADA status, and race) did not have a clinically meaningful effect on the dupilumab PK parameters in the AD population.

The subsequent asthma Pop PK analysis shared the AD Pop PK model structure and included data pooled from Phase 2 (Studies ACT11457 and DRI12544) and Phase 3 (Study EFC13579) studies in adult and adolescent patients with asthma.

The CRSwNP Pop PK strategy involved the development of a global Pop PK base model first with pooled data from healthy subjects and patients with AD and asthma patients (Study POH0668). This base model was then extended to allow the identification of covariates in a Pop PK model for the CRSwNP population using pooled data from Phase 2 and pivotal Phase 3 studies in adult patients with CRSwNP (Study POH0611).

The different studies performed are described hereafter.

a) Study POH0611

Title

Population Pharmacokinetic Analysis of Dupilumab Using Pooled Data from One Phase 2 and Two Phase 3 Studies in Patients with Nasal Polyposis

The main objectives of this analysis were to confirm and apply dupilumab global base population pharmacokinetic (Pop PK) model in CRSwNP patients, to assess the influence of intrinsic and extrinsic factors on dupilumab pharmacokinetics (PK) in NP patients and to predict individual dupilumab exposure in NP patients.

The analysis was conducted with data available up to two separate cut-off dates, one for Pop PK model development and covariate analysis and the other for individual exposure prediction in CRSwNP patients. Pop PK model development and covariate analysis in NP patients was conducted based on a pooled dataset including complete PK data from one Phase 2 study (ACT12340), as well as the partial data up to a Pop PK data cut-off date of Feb 12, 2018 from two pivotal Phase 3 studies (EFC14146 and EFC14280). The post-hoc estimates of individual PK steady-state exposure for each NP patient were generated based on a pooled dataset including complete PK data from study ACT12340 and clinical data after the latest clinical database lock (Sep 24, 2018) from two pivotal Phase 3 studies (EFC14146 and EFC14280).

A total of 466 CRSwNP patients and 2580 functional dupilumab concentration records were available in the Initial Dataset from the three studies used for CRSwNP Pop PK model development. Placebo data were excluded from the dataset.

Summary of PK data included in Pop PK model development

Phase	Study	Total number of patients[a]	Total number of PK samples collected[a]	Number of excluded PK samples				Number of excluded patients[d]	Number of patients included into Pop PK analysis	Number of PK samples included into Pop PK analysis
				Pre-dose and post-dose <LLOQ	Pre-dose >LLOQ	Outliers[b]	Dosing issue[c]			
2	ACT12340	30	290	70	0	0	--	0	30	220
3	EFC14146	142	769	212	0	2	2	1	141	553
3	EFC14280	294	1521	311	1	1	7	0	294	1201
Total		466	2580	593	1	3	9	1	465	1974

Abbreviation: LLOQ: Lower limit of quantitation.

Total number of patients and samples included in the initial dataset; [b] Outliers are defined in Section 2.6.1 ; [c] PK samples excluded due to dosing issue; [d] Concentration records for one patient (Patient No. 014146-840-0005-00101) in study EFC14146 were excluded as all samples were either <LLOQ or not measurable.

Pre-dose and post-dose samples that were BLQ (N=593), pre-dose samples above LLOQ (N=1), as well as dupilumab samples with dosing issue (N=9), were flagged and kept in the dataset and excluded by the analysis software. After database lock, an error was noted in the calibration curves

established during the quantification of plasma eotaxin-3. As a consequence, plasma eotaxin-3 was not tested as a covariate in the Pop PK analysis.

The pooled population was 61.9% male and age ranged from 19 to 83 years. CRSwNP patients had a relatively broader range of weight (38.0 to 150 kg).

Descriptive statistics of continuous covariates for NP patients in the Final Dataset

Covariate candidates	ACT12340			EFC14146			EFC14280			Total		
	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)
Weight (kg)	30	84.5 (16.6)	83.0 (55.2 – 126)	141	81.6 (18.0)	79.4 (38.0 – 130)	294	79.7 (17.9)	78.8 (39.4 – 150)	465	80.6 (17.9)	79.0 (38.0 – 150)
Age (Year)	30	48.0 (9.84)	48.7 (25.6 – 63.1)	141	50.8 (13.7)	52.4 (23.2 – 79.7)	294	52.7 (12.3)	52.3 (19.1 – 83.3)	465	51.8 (12.7)	52.0 (19.1 – 83.3)
CLCR (mL/min)	29[a]	119 (34.0)	109 (65.3 – 189)	141	124 (36.3)	116 (56.1 – 233)	294	128 (45.7)	121 (35.9 – 329)	464	127 (42.3)	120 (35.9 – 329)
CLCRN (mL/min/1.73 m2)	29[a]	103 (24.2)	97.2 (66.8 – 153)	141	110 (26.3)	108 (60.7 – 182)	294	116 (34.9)	110 (34.3 – 303)	464	114 (32.1)	109 (34.3 – 303)
Albumin (g/L)	30	42.7 (2.40)	42.0 (38.0 – 47.0)	141	46.1 (2.81)	46.0 (39.0 – 54.0)	294	45.0 (2.87)	45.0 (37.0 – 53.0)	465	45.2 (2.93)	45.0 (37.0 – 54.0)
EoS (cells/mm3)	30	406 (236)	355 (110 – 1190)	141	425 (313)	340 (0 – 2110)	294	423 (349)	330 (20.0 – 2900)	465	422 (332)	340 (0 – 2900)
NPS	30	5.87 (1.01)	6.0 (3.0 – 8.0)	141	5.65 (1.24)	5.50 (2.0 – 8.0)	294	6.18 (1.21)	6.0 (1.5 – 8.0)	465	6.00 (1.23)	6.00 (1.50 – 8.00)
NC	30	1.66 (0.73)	1.57 (0.6 – 3.0)	141	2.26 (0.58)	2.0 (1.0 – 3.0)	294	2.47 (0.59)	2.71 (0 – 3.0)	465	2.35 (0.63)	2.29 (0– 3.00)

Abbreviation: CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by BSA; EoS: eosinophil; NC:nasal congestion; NPS:nasal polyp score. N: subject number; SD: standard deviation.
a.One patient from study ACT12340 with missing information for CLCR and CLCRN was excluded from the summary. In the Pop PK analysis, the missing CLCR and CLCRN values for this patient were imputed using population median of CLCR and CLCRN.

Table 5 - Descriptive statistics of categorical covariates for NP patients in the Final Dataset

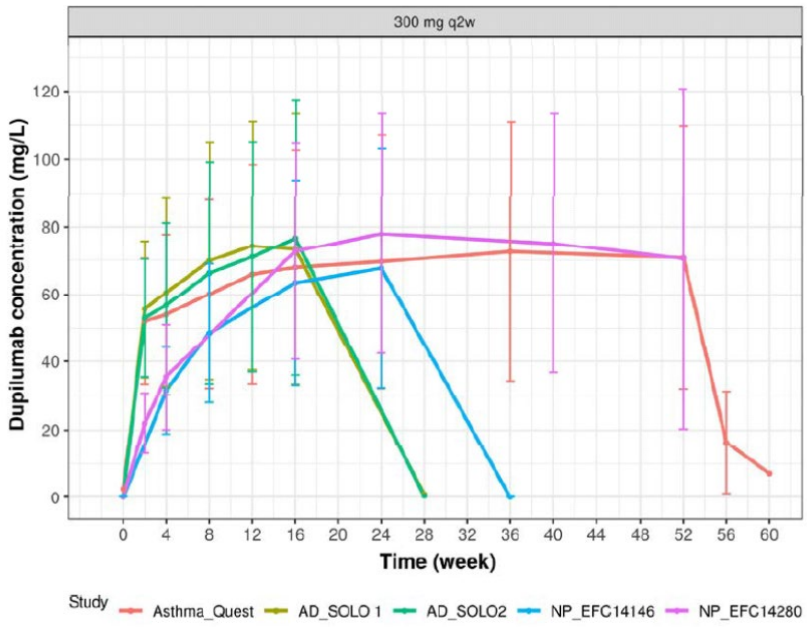
Covariate candidates	Subgroup	Act12340 N (%)	EFC14146 N (%)	EFC14280 N (%)	Total N (%)
Gender	Male	18 (60%)	87 (61.7%)	183 (62.2%)	288 (61.9%)
	Female	12 (40%)	54 (38.3%)	111 (37.8%)	177 (38.0%)
Race[a]	Caucasian	29 (96.7%)	136 (96.4%)	243 (82.7%)	408 (87.7%)
	Black	1 (3.3%)	2 (1.4%)	4 (1.4%)	7 (1.5%)
	Asian	0 (0%)	1 (0.7%)	36 (12.2%)	37 (8.0%)
	Other	0 (0%)	1 (0.7%)	10 (3.4%)	11 (2.4%)
	Missing	0 (0%)	1 (0.7%)	1 (0.3%)	2 (0.4%)
Stationary ADA	Negative	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Pre-existing	7 (23.3%)	1 (0.7%)	8 (2.7%)	16 (3.4%)
	Treatment-emergent	3 (10%)	3 (2.1%)	12 (4.1%)	18 (3.9%)
	Treatment-boosted	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stationary ADA	Non-positive	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Positive	10 (33.3%)	4 (2.8%)	20 (6.8%)	34 (7.3%)
Stationary ADA	Negative ADA	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	0< titers <1000	7 (23.3%)	4 (2.8%)	17 (5.8%)	28 (6.0%)
	1000<= titers <=10000	3 (10%)	0 (0%)	0 (0%)	3 (0.6%)
	titers >10000	0 (0%)	0 (0%)	3 (1.0%)	3 (0.6%)
UPSIT[b]	Normal loss of smell	0 (0%)	4 (2.8%)	5 (1.7%)	9 (1.9%)
	Mild hyposmia	0 (0%)	8 (5.7%)	11 (3.7%)	19 (4.1%)
	Moderate hyposmia	0 (0%)	9 (6.4%)	15 (5.1%)	24 (5.2%)
	Severe hyposmia	0 (0%)	15 (10.6%)	28 (9.5%)	43 (9.2%)
	Anosmia	30 (100%)	100 (70.9%)	218 (74.1%)	348 (74.8%)
	Missing	0 (0%)	5 (3.5%)	17 (5.8%)	22 (4.7%)
ASTH	With	16 (53.3%)	80 (56.7%)	176 (59.9%)	272 (58.5%)
	Without	14 (46.7%)	61 (43.3%)	118 (40.1%)	193 (41.5%)
INCS	Once a day	2 (6.7%)	10 (7.1%)	58 (19.7%)	70 (15.1%)
	Twice a day	28 (93.3%)	131 (92.9%)	236 (80.3%)	395 (85.0%)
ANTIH	With	4 (13.3%)	11 (7.8%)	49 (16.7%)	64 (13.8%)
	Without	26 (86.7%)	130 (92.2%)	245 (83.3%)	401 (86.2%)
OCS	With	1 (3.3%)	87 (61.7%)	225 (76.5%)	313 (67.3%)
	Without	29 (96.7%)	54 (38.3%)	69 (23.5%)	152 (32.7%)
ALLE	With	0 (0%)	2 (1.4%)	8 (2.7%)	10 (2.15%)
	Without	30 (100%)	139 (98.6%)	286 (97.3%)	455 (97.85%)

Abbreviation: ADA: anti-drug antibody; ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; ASTH: patients with comorbid asthma; INCS: intranasal corticosteroid spray; OCS: oral corticosteroids; UPSIT: university of Pennsylvania smell identification test.
a. Two patients from studies EFC14146 and EFC14280 had missing information for race. In Pop PK analysis, the missing race values those patients were imputed using the categorical value of the majority population.
b. Five patients from study EFC14146 and 17 patients form EFC14280 had missing information for UPSIT. In Pop PK analysis, the missing UPSIT values for those patients were imputed using the categorical value of the majority population.

Base model selection

The observed mean dupilumab concentration time profiles for CRSwNP patients who received 300 mg q2w in studies EFC14146 and EFC14280 were compared to the observed profiles for AD and asthma patients who received 300 mg q2w (with a loading dose of 600 mg) from three phase 3 studies (studies AD-1334, AD-1416 and EFC13579). The observed PK data confirmed the similarity dupilumab PK profiles across adult AD, asthma and CRSwNP populations.

Figure 3 - Observed mean concentration of Dupilumab (±SD) versus nominal time for NP patients (300 mg q2w), AD and asthma patients (300 mg q2w with a loading dose of 600 mg)



Abbreviation: AD_SOLO 1: study AD-1614; AD_SOLO 2: study AD-1224; Asthma_Quest: study EFC13579; q2w: every two weeks.

The adequacy of global Pop PK base model to describe dupilumab PK in CRSwNP patients was initially evaluated by comparing the observed concentrations and the predicted concentrations from global Pop PK base model by a maximum a posteriori (MAP) bayesian estimation approach. The mean values of population prediction error and absolute population prediction error for all the concentrations from the 3 studies at weeks 4- 24 were 13.6% and 33.6%, respectively. This indicates a reasonable applicability of global Pop PK base model to be used as the start point of NP Pop PK base model selection.

The final CRSwNP Pop PK base model was selected due to good precision of parameter estimates and good model performance. This was a two-compartment model with first order absorption, and parallel linear and nonlinear elimination. Most PK parameters (except for V2, Ke, and Vmax) were fixed to values estimated with data from clinical studies in HV, AD and asthma patients. IIV was estimated for Ke and random effect parameters were estimated.

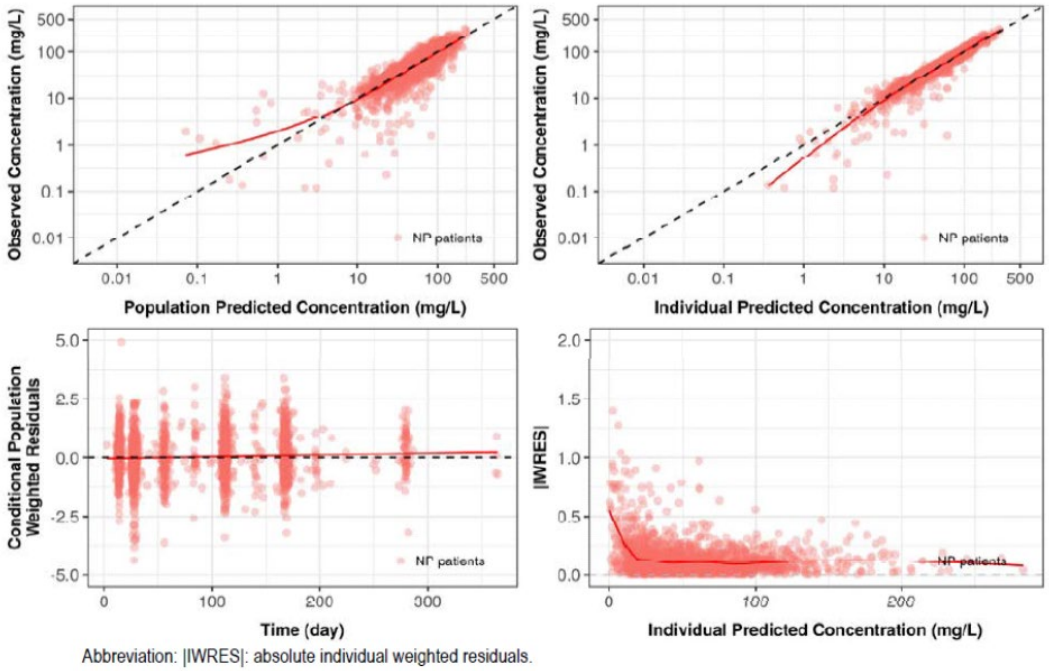
Among the tested covariates, only body weight was identified to be a statistical significant covariate on dupilumab PK in NP patients. The final CRSwNP Pop PK model included weight as a covariate on central compartment (V2), first order elimination rate constant (Ke), and maximum nonlinear eliminate rate (Vmax).

Table 9 - Parameter estimates for final NP Pop PK base model

Parameter	Estimate	% RSE	[95%CI]
Typical value of K_e (θ_1, 1/day)	0.0367	1.72%	[0.0354, 0.0380]
Typical value of V_2 (θ_2, L)	3.08	1.61%	[2.98, 3.18]
Typical value of K_{23} (θ_3, 1/day)	0.089 (fix)	--	--
Typical value of K_{32} (θ_4, 1/day)	0.15 (fix)	--	--
Typical value of V_{max} (θ_5, mg/L/day)	1.16	4.60%	[1.06,1.27]
Typical value of K_m (θ_6, mg/L)	2.52 (fix)	--	--
Typical value of K_a (θ_7, 1/day)	0.25 (fix)	--	--
Typical value of F_{sc} (θ_8, %)	62.8 (fix)	--	--
Power coefficient of weight on K_e	0.12 (fix)	--	--
Power coefficient of weight on V_2	0.72 (fix)	--	--
Power coefficient of weight on V_{max}	0.33 (fix)	--	--
Inter-individual variability (CV%)			
Parameter	**Estimate**	**% RSE**	**[95%CI]**
K_e	17.2	19.6%	[13.4, 20.3]
V_2	8.09 (fix)	--	--
V_{max}	29.1 (fix)	--	--
K_a	44.0 (fix)	--	--
F_{sc}	41.9 (fix)	--	--
Residual variability (RV)			
Proportional term	0.156	3.15%	[0.151, 0.160]
Additive term (mg/L)	3.40	8.72%	[3.09, 3.68]
Derived Parameters			
CL (L/day)	0.113	--	--
Q (L/day)	0.274	--	--
V_3 (L)	1.83	--	--
V_{ss} (L)	4.91	--	--

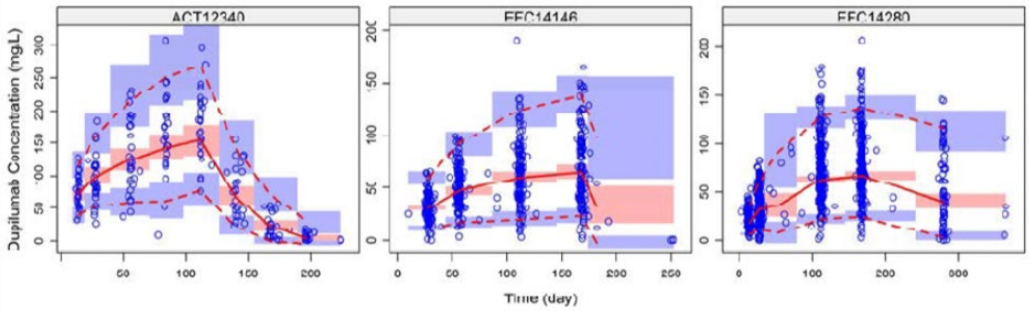
Abbreviation: CI: confidence interval; CL: linear clearance; CV: coefficient of variation; F_{sc}: bioavailability; K_{23}, K_{32}: inter-compartment distribution rate constants; K_a : absorption rate constant ; K_e: linear elimination rate constant; K_m: Michaelis constant; V_2:volume of central compartment; V_3: volume of peripheral compartment; V_{max}: maximum target-mediated rate of elimination; V_{ss}: Volume distribution at steady state; Q: inter-compartment distribution clearance; %RSE: percentage of relative standard error (100% * SE / estimate); θ: estimate of a Pop PK parameter.

Figure 4 - Goodness-of-fit plots from final NP Pop PK base model



Abbreviation: |IWRES|: absolute individual weighted residuals.

Figure 6 - Visual predictive checks for final NP Pop PK model by study



Note: Legend: blue dots: observations; solid and read dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; pink and light blue areas: confidence intervals of median and centiles of predicted concentrations at each time bin.

Impact of covariates

The descriptive summary of steady-state exposures of dupilumab after 300 mg qw (with a loading dose of 600 mg) and 300 mg q2w repeated doses in Phase 2 and 3 studies (ACT12340, EFC14146 and EFC14280) as a function of tested covariates is provided in Table 14 for both continuous and categorical covariate candidates. The apparent difference in PK exposures across age, race and CLCR groups is mainly explained by the difference in the body weight. The descriptive summary of steady-state exposures of dupilumab after 300 mg q2w-q4w as a function of weight category is provided in Table 15. The impact of comorbidity (asthma) and concomitant medications on dupilumab PK exposures was found to be minimal, as shown in Table 16.

A graphical representation of steady-state dupilumab exposures after 300 mg q2w repeated dosing in two phase 3 studies by covariates is provided in Figure 8. Similarly, the impact of comorbidity and concomitant medications on dupilumab PK exposures is shown in Figure 9.

Table 14 - Mean (SD) steady-state exposures for NP patients in Phase 2 and 3 studies (ACT12340, EFC14146 and EFC14280) as a function of tested covariates

Tested Covariates		300 mg q2w (EFC14146 and EFC14280)				300 mg qw with a loading dose of 600 mg (ACT12340)			
		N[a] (median weight)	$AUC_{\tau,ss}$[c] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	N[a] (median weight)	$AUC_{\tau,ss}$[c] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
All	--	420 (78.7 kg)	1202 (456)	94.0 (33.8)	72.5 (30.3)	28 (83.0 kg)	1210 (360)	177 (52.2)	165 (49.9)
Weight (kg)	< 70	122 (62.1 kg)	1618 (431)	125 (31.6)	99.6 (28.9)	4 (64.7 kg)	1435 (567)	210 (82.0)	195 (78.7)
	≥ 70 - < 90	178 (79.0 kg)	1170 (328)	91.7 (23.9)	70.3 (22.2)	16 (81.0 kg)	1245 (305)	182 (44.1)	169 (42.2)
	≥ 90	120 (99.0 kg)	827 (256)	65.7 (18.8)	48.3 (17.3)	8 (104 kg)	1029 (309)	150 (44.6)	140 (42.8)
Age (year)	≥ 18 - < 65	344 (80.0 kg)	1201 (465)	93.8 (34.5)	72.5 (30.7)	28 (83.0 kg)	1210 (360)	177 (52.2)	165 (49.9)
	≥ 65 - < 75	65 (73.0 kg)	1181 (423)	92.8 (31.1)	70.9 (28.6)	0	--	--	--
	≥ 75	11 (70.0 kg)	1377 (369)	107 (26.6)	84.9 (26.0)	0	--	--	--
Gender	Male	258 (83.4 kg)	1101 (371)	86.3 (27.3)	66.2 (25.0)	17 (86.3 kg)	1179 (296)	172 (42.6)	160 (41.4)
	Female	162 (70.0 kg)	1363 (529)	106 (39.1)	82.7 (35.0)	11 (78.9 kg)	1259 (454)	184 (66.0)	171 (62.5)
Race[e]	Caucasian	366 (79.9 kg)	1179 (447)	92.3 (33.1)	71. (29.7)	27 (83.0 kg)	1224 (360)	179 (52.1)	166 (50.0)
	Black	5 (105.4 kg)	878 (438)	69.6 (33.)	51.4 (28.3)	1 (78.9 kg)	850	122.9	118.2
	Asian	36 (64.3 kg)	1489 (452)	115 (33.4)	91.3 (30.0)	0	--	--	--
	Other	11 (85.3 kg)	1196 (487)	93.1 (35.9)	72.3 (32.3)	0	--	--	--
Ethnicity[e]	Japanese	36 (64.3 kg)	1489 (452)	115 (33.4)	91.3 (30.)	0	--	--	--
	Non-Japanese	382 (80. kg)	1176 (449)	92.1 (33.2)	70.8 (29.8)	28 (79.0 kg)	1210 (360)	177 (52.2)	165 (49.9)
Albumin (g/L)	≥ 30 - < 40	9 (75.0 kg)	1023 (466)	82. (34.1)	59.2 (30.0)	2 (90.1 kg)	1230 (537)	179 (79.0)	169 (71.3)
	≥ 40 - < 50	382 (79.2 kg)	1196 (451)	93.5 (33.4)	72.2 (29.9)	26 (83.0 kg)	1209 (359)	177 (51.9)	164 (49.8)
	≥ 50	29 (72.0 kg)	1340 (511)	104 (38.3)	81.5 (33.6)	0	--	--	--
CLCR[f] (mL/min)	≥ 30 - < 60	9 (67.0 kg)	1633 (511)	126. (37.3)	102 (34.8)	0	--	--	--
	≥ 60 - < 90	62 (65.0 kg)	1544 (466)	119 (34.3)	94.9 (31.3)	4 (80.0 kg)	1312 (292)	191 (42.4)	179 (40.6)
	≥ 90	349 (82.0 kg)	1130 (419)	88.7 (31.1)	67.8 (27.8)	23 (84.0 kg)	1204 (378)	176 (54.7)	163 (52.3)

CLCRN[f] (mL/min/1.73 m²)	≥ 30 - < 60	8 (67.5 kg)	1658 (555)	127 (40.9)	104 (37.6)	0	–	–	–
	≥ 60 - < 90	81 (71.0 kg)	1309 (460)	102 (33.7)	79.6 (31.0)	11 (82.9 kg)	1261 (310)	184 (45.0)	173 (42.7)
	≥ 90	331 (81.0 kg)	1165 (444)	91.3 (33.)	70. (29.3)	16 (84.7 kg)	1191 (404)	175 (58.5)	161 (55.9)
Stationary ADA	Negative ADA	373 (78. kg)	1229 (453)	96. (33.5)	74.4 (30.1)	19 (83.6 kg)	1218 (326)	178 (47.1)	166 (45.3)
	positive ADA	47 (83. kg)	987 (428)	78.1 (31.8)	58.1 (28.0)	9 (79.0 kg)	1194 (446)	175 (64.8)	163 (61.4)
Stationary ADA	Negative	373 (78. kg)	1229 (453)	96. (33.5)	74.4 (30.1)	19 (83.6 kg)	1218 (326)	178 (47.1)	166 (45.3)
	Pre-existing	9 (77.8 kg)	1147 (359)	90.2 (26.6)	68.7 (24.0)	6 (81.0 kg)	1379 (437)	202 (63.5)	188 (60.4)
	Treatment-emergent	38 (86.8 kg)	949 (438)	75.2 (32.6)	55.6 (28.6)	3 (78.9 kg)	824 (90.8)	121 (14.3)	112 (11.3)
Stationary ADA	Negative ADA	373 (78.0 kg)	1229 (453)	96. (33.5)	74.4 (30.1)	19 (83.6 kg)	1218 (326)	178 (47.1)	166 (45.3)
	0< titers <1000	44 (82.5 kg)	1024 (416)	80.8 (31.1)	60.6 (27.1)	6 (83.6 kg)	1118 (354)	163 (51.9)	153 (48.2)
	1000<= titers <=10000	1 (91.5 kg)	418	36.6	19.2	3 (76.0 kg)	1347 (656)	198 (94.)	181 (92.0)
	titers >10000	2[g] (104 kg)	445	38.8	21.9	0	–	–	–

Abbreviation: ADA: antidrug antibody; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to τ at steady state; CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by BSA; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; N: subject number after excuding the discontinued patients; qw: every week; q2w: every two weeks.
a. Six discontinued patients out of 141 patients (before week 22) in study EFC14146 and 9 discontinued patients out of 294 patients (before week 22) in study EFC14280 were excluded in this statistical summary table.
b. Two discontinued patients out of 30 patients (before week 15) in study ACT12340 were excluded in this statistical summary table.
c. $AUC_{\tau,ss}$ = AUC[week 22 – week 24] for 300 mg q2w from Studies from studies EFC14146 and EFC14280;
d. $AUC_{\tau,ss}$ = AUC[week 15 – week 16] for 300 mg qw (with a loading dose of 600 mg) from study ACT12340.
e. One patient from study EFC14146 and one patient from study EFC14280 with missing information for Race and Ethnicity were excluded from the summary.
f. One patient from study ACT12340 with missing information for CLCR and CLCRN was excluded from the summary.
g. In the Final dataset, there are 3 patients in studies EFC14146 and EFC14280 with high titer >10000. However 1 patient was discontinued at week 20 and excluded from the summary.

Table 15 - Mean (SD) steady-state exposures for NP patients receiving 300 mg q2w-q4w regimen in study EFC14280 as a function of body weight

Covariate			300 mg q2w-q4w (EFC14280)		
		N[a] (median weight)	$AUC_{\tau,ss}$ [b] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
All	–	141 (77.6 kg)	929 (483)	46.5 (19.6)	17.9 (13.7)
Weight (kg)	< 70	45 (63 kg)	1286 (480)	61.5 (19.1)	27.6 (14.2)
	≥ 70 - < 90	57 (78 kg)	934 (367)	46.6 (14.4)	17.9 (10.7)
	≥ 90	39 (98 kg)	511 (256)	29. (10.3)	6.73 (7.06)

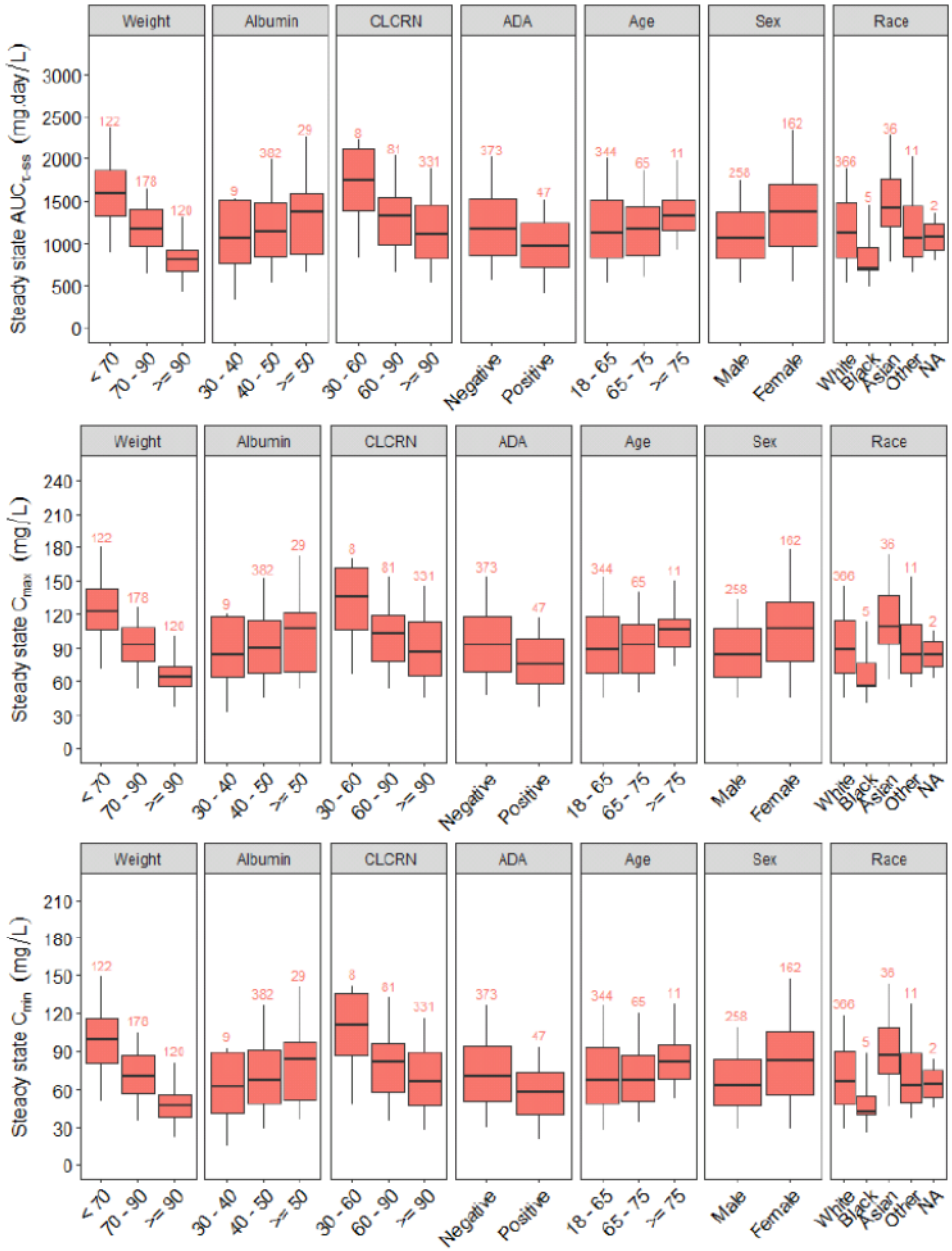
Abbreviation: ; ADA: antidrug antibody; ; AUC□,ss: area under the concentration time curve from time 0 to □ at steady state; Cmax,ss: maximum concentration at steady state; Cmin,ss: minimum concentration at steady state; N: subject number after excuding the discontinued patientsq2w: every two week; q4w: every four weeks; 300 mg q2w-q4w:300 mg q2w until Week 24, then 300 mg q4w until Week 52.
a. Five discontinued patients out of 146 (before week 48) in the arm of 300 mg q2w-q4w in study EFC14280 were excluded in this statistical summary table.
b. AUC□,ss = AUC[week 48 – week 52] for 300 mg q2w-q4w from study EFC14280. were excluded in this statistical summary table.

Table 16 - The impact of comorbidity and concomitant medications on mean (SD) exposures in NP patients from Phase 2 and 3 studies

Comorbidity and Concomitant medication		300 mg q2w (EFC14146 and EFC14280)				300 mg qw with a loading dose of 600 mg (ACT12340)			
		N[a]	$AUC_{\tau,ss}$ [b] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	N[c]	$AUC_{\tau,ss}$ [d] (mg.day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
All	–	420	1202 (456)	94.0 (33.8)	72.5 (30.3)	28	1210 (360)	177 (52.2)	165 (49.9)
ASTH	With	248	1236 (458)	96.6 (34.0)	74.6 (30.3)	15	1284 (371)	187 (53.9)	175 (51.2)
	Without	172	1154 (451)	90.3 (33.3)	69.5 (30.1)	13	1125 (342)	165 (49.4)	153 (47.4)
ANTIH	With	61	1277 (533)	99.5 (39.5)	77.7 (35.3)	4	1425 (322.6)	208 (46.9)	194 (44.6)
	Without	359	1189 (442)	93.1 (32.7)	71.7 (29.3)	24	1174 (359.9)	172 (52.1)	160 (49.9)
INCS	Once a day	60	1344 (469)	104 (34.8)	81.8 (31.0)	1	1267	186	172
	Twice a day	360	1179 (450)	92.3 (33.4)	71. (29.9)	27	1208 (367)	176 (53.2)	164 (50.8)
ALLE	With	10	1168 (449)	90.9 (33.6)	70.9 (29.5)	28	1210 (360)	177 (52.2)	165 (49.9)
	Without	410	1203 (457)	94.1 (33.8)	72.6 (30.3)	0	–	–	–
OCS	With	311	1202 (448)	93.9 (33.2)	72.6 (29.8)	1	975	143	131
	Without	109	1203 (481)	94.2 (35.6)	72.4 (31.8)	27	1219 (364)	178 (52.8)	166 (50.4)

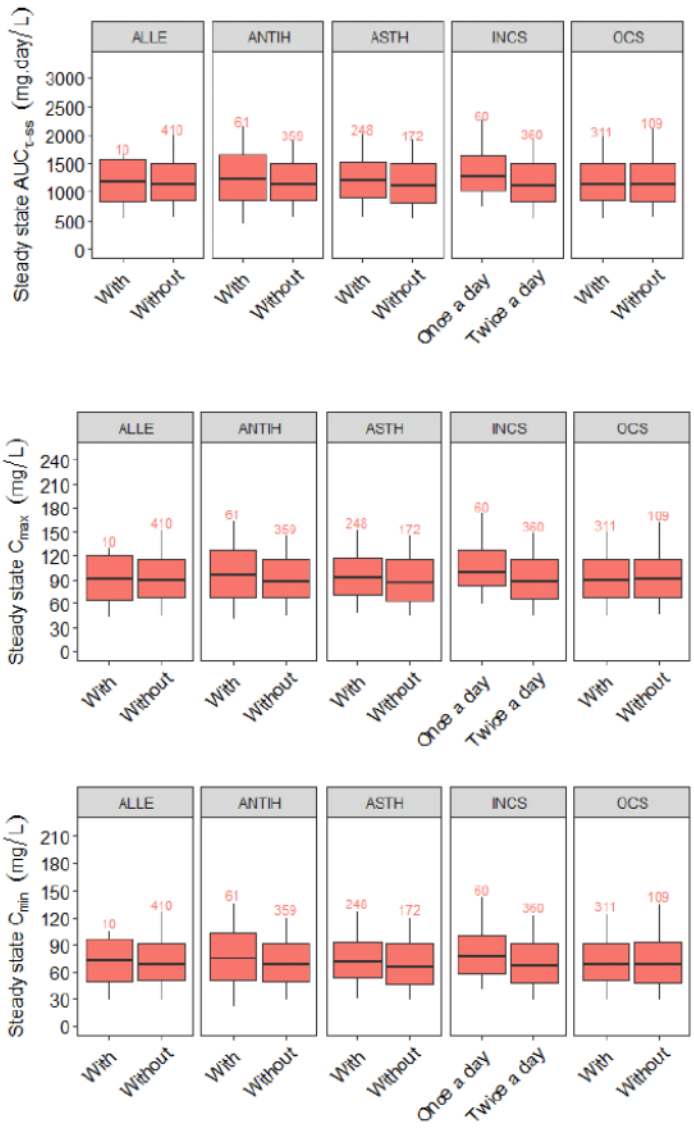
Abbreviation: ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; ASTH: patients with comorbid asthma; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to t at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; N: subject number after excluding the discontinued patients; INCS: intranasal corticosteroid spray; OCS: oral corticosteroids; qw: every week; q2w: every two weeks.
a. Six discontinued patients out of 141 patients (before week 22) in study EFC14146 and 9 discontinued patients out of 294 patients (before week 22) in study EFC14280 were excluded in this statistical summary table.
b. $AUC_{\tau,ss}$ = AUC[week 22 – week 24] for 300 mg q2w from studies EFC14146 and EFC14280.
c. Two discontinued patients out of 30 patients (before week 15) in study ACT12340 were excluded in this statistical summary table.
d. $AUC_{\tau,ss}$ = AUC[week 15 – week 16] for 300 mg qw (with a loading dose of 600 mg) from study ACT12340.

Figure 8 - Boxplot of dupilumab $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ in NP patients who received 300 mg q2w in two Phase 3 studies (EFC14146 and EFC14280) by tested covariates



Note: Lower and upper end of whisker indicated 5th and 95th percentile of $AUC_{\tau,ss}$ $C_{max,ss}$ and $C_{min,ss}$. Number inside plot panel indicate patient numbers in each bin of covariate; Weight (kg), Albumin (g/L), CLCRN = creatinine clearance (mL/min/1.73 m^2), Age (year), Negative ADA = negative ADA at all the time, Positive ADA = positive ADA at any time, NA=not available, representing the missing information of race in 2 patients. $AUC_{\tau,ss}$: area under the concentration time curve from 0 to τ at steady state (week 22 to week 24); $C_{max,ss}$: maximum concentration at steady state ; $C_{min,ss}$: minimum concentration at steady state; q2w: every two weeks.

Figure 9 - Boxplot of dupilumab $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ in NP patients who received 300 mg q2w in two Phase 3 studies (EFC14146 and EFC14280) by comorbidity and concomitant medications



Note: NP patients received 300 mg q2w in two phase 3 studies EFC14146 and EFC14280). Lower and upper end of whisker indicated 5th and 95th percentile of $C_{min,ss}$; number inside plot panel indicate the counts of patients in each bin of comorbidity and concomitant medication: ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to τ at steady state (week 22 to week 24); $C_{max,ss}$: maximum concentration at steady state ; $C_{min,ss}$: minimum concentration at steady state;INCS: intranasal corticosteroid spray; OCS: oral corticosteroids; q2w: every two weeks.

Pop PK model based simulations

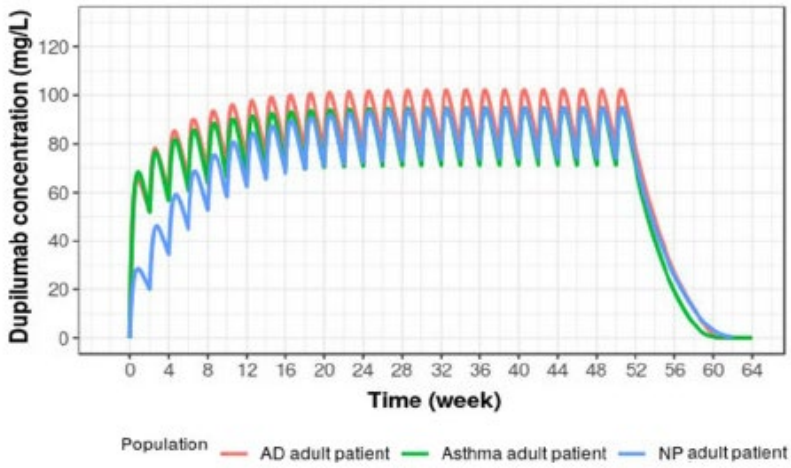
Simulated typical PK profiles after different dupilumab regimens

The concentration-time profiles for dupilumab were simulated for a typical patient (body weight 79 kg [median weight of Final Dataset]) for two treatment regimens (300 mg q2w and 300 mg q2w-q4w) in study EFC14280. These simulations were used to determine the time to achieve steady state (i.e., achieving 90% of Cmin,ss), as well as time for concentration to fall below LLOQ.

Furthermore dupilumab concentration-time profiles at 300 mg q2w in adult CRSwNP patients with no loading dose was compared to those in adult asthma and AD patients with a loading dose of 600 mg. The increase in dupilumab concentrations with repeated dosing in CRSwNP patients was slower than in AD and asthma patients due to the absence of the loading dose in CRSwNP patients.

However, dupilumab concentration-over-time profiles in typical CRSwNP, asthma or AD patients, as predicted from the respective CRSwNP, asthma and AD Pop PK models, are highly comparable.

Comparison of dupilumab typical concentration-time profiles in adult patients with NP (300 mg q2w without loading dose) and asthma and AD (300 mg q2w with a loading dose of 600 mg)

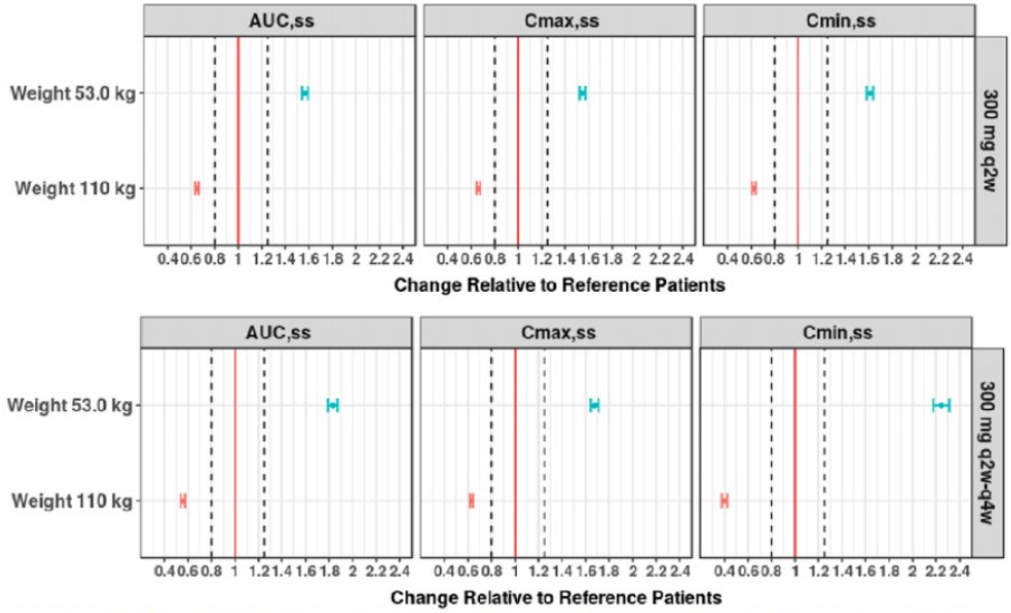


Simulations were also conducted to assess the impact of weight on steady-state exposures of dupilumab for treatment arms 300 mg q2w and 300 mg q2w-q4w.

Impact of weight on dupilumab exposures

A forest plot illustrating the impact of weight on steady state dupilumab exposure variables over the range of the 5th to 95th percentiles of body weights relative to a typical patient is shown in Figure 13. The results are summarised in Table 17. The results confirm the notable effect of weight on dupilumab steady state exposure in NP patients.

Figure 13 - Forest plot of the impact of weight on steady state exposures of dupilumab following 300 mg q2w or 300 mg q2w-q4w regimens in NP patients



Typical patients: body weight of 79.0 kg. Treatment: 300 mg q2w represents 300 mg q2w until week 52; 300 mg q2w-q4w represents 300 mg q2w until Week 24, then 300 mg q4w until Week 52. The covariate value for simulation (n = 1000) represented 5% and 95% percentile of the covariates distribution of population PK population. Dupilumab mean steady state exposures (i.e. $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$) for the simulated typical patients are represented by the red solid vertical line. The black dashed vertical lines represent 80 and 125% of the typical mean steady state exposures (i.e. $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$) for simulated patients. The solid square and error bars represent the mean and 90% confidence interval for the fold change of dupilumab steady state exposures (i.e. $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$) in simulated patients relative to the typical patients.

Abbreviation: $AUC_{\tau,ss}$: Area under the concentration time curve from time 0 to τ at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; q2w: every two weeks; q4w: every four weeks.

Table 17 - Impact of weight on dupilumab exposures in NP patients at 300 mg q2w

Treatment	PK exposure	Population	Weight	Mean	SD	Change Relative to Typical Patient	N
300 mg q2w	$AUC_{\tau,ss}$	Median (typical patient)	79.0 kg	1130.7	340.9	--	1000
		95% percentile	110 kg	733.9	260	-35.1%	1000
		5% percentile	53.0 kg	1773	472.9	56.8%	1000
	$C_{min,ss}$	Median (typical patient)	79.0 kg	68.6	22.9	--	1000
		95% percentile	110 kg	42.8	17.4	-37.6%	1000
		5% percentile	53.0 kg	110.6	32.0	61.2%	1000
	$C_{max,ss}$	Median (typical patient)	79.0 kg	88.9	25.6	--	1000
		95% percentile	110 kg	58.8	19.6	-33.9%	1000
		5% percentile	53.0 kg	137.4	35.5	54.6%	1000
300 mg q2w-q4w	$AUC_{\tau,ss}$	Median (typical patient)	79.0 kg	821	356	--	1000
		95% percentile	110 kg	458	413	-44.3%	1000
		5% percentile	53.0 kg	1504	1457	83.2%	1000
	$C_{min,ss}$	Median (typical patient)	79.0 kg	15.3	10.5	--	1000
		95% percentile	110 kg	6.14	6.05	-59.9%	1000
		5% percentile	53.0 kg	34.3	16.2	124%	1000
	$C_{max,ss}$	Median (typical patient)	79.0 kg	42.3	15.0	--	1000
		95% percentile	110 kg	26.7	9.95	-37.0%	1000
		5% percentile	53.0 kg	71.0	22.0	67.8%	1000

Abbreviation: $AUC_{\tau,ss}$: Area under the concentration time curve from time 0 to τ at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; N: subject number in simulation; q2w: every two weeks; q4w: every four weeks; 300 mg q2w-q4w:300 mg q2w until Week 24, then 300 mg q4w until Week 52.

Final pop PK estimates for the CRSwNP population:

Table IV – Dupilumab final NP Pop PK model parameters

Parameter	Estimate	% RSE	[95%CI]
Typical value of K_e (θ_1, 1/day)	0.0367	1.72%	[0.0354, 0.0380]
Typical value of V_2 (θ_2, L)	3.08	1.61%	[2.98, 3.18]
Typical value of K_{23} (θ_3, 1/day)	0.089 (fix)	--	–
Typical value of K_{32} (θ_4, 1/day)	0.15 (fix)	--	–
Typical value of V_{max} (θ_5, mg/L/day)	1.16	4.60%	[1.06,1.27]
Typical value of K_m (θ_6, mg/L)	2.52 (fix)	--	–
Typical value of K_a (θ_7, 1/day)	0.25 (fix)	--	–
Typical value of F_{SC} ($\theta_{8,\%}$)	62.8 (fix)	--	–
Power coefficient of weight on K_e	0.12 (fix)	--	–
Power coefficient of weight on V_2	0.72 (fix)	--	–
Power coefficient of weight on V_{max}	0.33 (fix)	--	–
Inter-individual variability (CV%)			
Parameter	**Estimate**	**% RSE**	**[95%CI]**
K_e	17.2	19.6%	[13.4, 20.3]
V_2	8.09 (fix)	–	–
V_{max}	29.1 (fix)	–	–
K_a	44.0 (fix)	–	–
F_{SC}	41.9 (fix)	–	–
Residual variability (RV)			
Proportional term	0.156	3.15%	[0.151, 0.160]
Additive term (mg/L)	3.40	8.72%	[3.09, 3.68]
Derived parameters			
CL (L/day)	0.113	–	–
Q (L/day)	0.274	–	–
V_3 (L)	1.83		
V_{ss} (L)	4.91	–	–

Abbreviation: CI: confidence interval; CL: linear clearance; CV: coefficient of variation; F_{SC}: bioavailability; K_{23}, K_{32}: inter-compartment distribution rate constants; K_a: absorption rate constant ; K_e: linear elimination rate constant; K_m: Michaelis constant; V_2:volume of central compartment; V_3: volume of peripheral compartment; V_{max}: maximum target-mediated rate of elimination; V_{ss}: volume distribution at steady state; Q: inter-compartment distribution clearance; %RSE: Percentage of relative standard error (100% * SE / estimate); θ: estimate of a Pop PK parameter.

b) Study POH0668

Title

Dupilumab Global Population Pharmacokinetic Base Model Development Using Pooled Data from Atopic Dermatitis Patients, Asthma Patients, and Healthy Subjects

The main objective of this analysis was to develop and qualify a global population pharmacokinetic (Pop PK) base model for dupilumab in atopic dermatitis (AD) and asthma patients.

Concentrations of functional dupilumab in serum from 20 Phase 1, 2 and 3 studies, with Phase 1 studies in healthy subjects (HV) after a single intravenous (IV) or subcutaneous (SC) administration of dupilumab and Phase 2 and 3 studies in AD and asthma patients, after repeated SC administration of dupilumab once every week (qw), two weeks (q2w) or four weeks (q4w), were included.

Summary of clinical studies included in the analysis

Phase	Study	Dupilumab Dose Regimens	Duration of Treatment	Population	PK Sampling	Number of Study Subjects			Study Status for Pop PK analysis
						Total	Included for Pop PK analysis	Excluded for Pop PK analysis	
1	AS-0907	IV : 1, 3, 8 and 12 mg/kg; SC : 150 and 300 mg	Single dose	Healthy adults	Dense sampling	36[a]	36[a]	0[a]	Completed[a]
1	HV-1108	SC : 300 mg	Single dose		Dense sampling	36[a]	36[a]	0[a]	Completed[a]
1	TDU12265	SC : 75, 150, 300 and 600 mg	Single dose		Dense sampling	24[a]	24[a]	0[a]	Completed[a]
1	PKM12350	SC : 300 mg	Single dose		Dense sampling	30[a]	30[a]	0[a]	Completed[a]
1	PKM14161	SC : 300 mg	Single dose		Dense sampling	38[a]	38[a]	0[a]	Completed[a]
1	PKM14271	SC : 200 mg	Single dose		Dense sampling	38[a]	38[a]	0[a]	Completed[a]
1b	AD-0914	SC : 75, 150, 300 mg qw	4 weeks	Adult AD patients	Sparse sampling	24[a]	20[a]	4[a]	Completed[a]
2a	AD-1026	SC : 150, 300 mg qw	4 weeks		Sparse sampling	27[a]	26[a]	1[a]	Completed[a]
2a	AD-1117	SC : 300 mg qw	12 weeks		Sparse sampling	55[a]	52[a]	3[a]	Completed[a]
2a	AD-1121	SC : 300 mg qw	4 weeks		Sparse sampling	21[a]	21[a]	0[a]	Completed[a]
2b	AD-1021	SC : 100 mg q4w, 200 mg q2w (with a loading dose of 400 mg) and 300 mg q4w, q2w, qw (with a loading dose of 600 mg)	16 weeks		Sparse sampling	318[a]	304[a]	14[a]	Completed[a]
2b	AD-1307	SC : 200 mg qw (with a loading dose of 400 mg)	16 weeks		Sparse sampling	27[a]	25[a]	2[a]	Completed[a]
2	AD-1314	SC : 300 mg qw (with a loading dose of 600 mg)	16 weeks		Sparse sampling	97[a]	93[a]	4[a]	Completed[a]
3	AD-1334 (SOLO 1)	SC : 300 mg qw, q2w (with a loading dose of 600 mg)	16 weeks		Sparse sampling[a]	447[a]	428[a]	19[a]	Completed[a]
3	AD-1416 (SOLO 2)	SC : 300 mg qw, q2w (with a loading dose of 600 mg)	16 weeks		Sparse sampling[a]	473[a]	460[a]	13[a]	Completed[a]
3	AD-1224 (Chronos)	SC : 300 mg qw, q2w (with a loading dose of 600 mg)	52 weeks		Sparse sampling[a]	424[a]	410[a]	14[a]	Partial[a]
2a	ACT11457	SC : 300 mg qw	12 weeks	Adult and adolescent asthma patients	Sparse sampling[b]	52[b]	52[b]	0[b]	Completed[b]
2b	DRI12544	SC : 300mg q2w, q4w (with a 600 mg loading dose) and 200 mg q2w, q4w (with a 400 mg loading dose)	24 weeks		Sparse sampling[b]	611[b]	603[b]	8[b]	Completed[b]
3	EFC13579 (Quest)	SC : 300 mg q2w (with a 600 mg loading dose) and 200 mg q2w (with a 400 mg loading dose)	52 weeks		Sparse sampling[b]	1260[b]	1257[b]	3[b]	Partial[b]
3	EFC13691[c] (Venture)	SC : 300 mg q2w (with a 600 mg loading dose)	24 weeks		Sparse sampling[b]	103[b]	103[b]	0[b]	Partial[b]
Total	--	--	--	--	--	4141	4056[d]	85	--

a. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1)
b. Source document : asthma Pop PK report (POH0530)
c. PK data from Study EFC13691 were not included for asthma Pop PK model development (POH0530), but were included for the current global Pop PK base model development
d. Number exposed to dupilumab in each study included for current Pop PK base model development; total N = 4056, with 202 adult HV and 1839 AD patients as well as 2015 asthma patients (including 69 adolescents ≥12 to <18 years of age)

A total of 4141 individuals (i.e., 202 HV, 1913 AD patients, and 2026 asthma patients) and 38759 functional dupilumab concentration records were available in the Initial pooled Dataset from the 20 studies used for global Pop PK model development. Following exclusion of concentrations below the lower limit of quantitation, LLOQ (BLQ), pre-dose measurable concentrations and outlier concentrations, the Final Dataset contained 30557 dupilumab samples from 4056 subjects (including 69 adolescents).

Descriptive statistics of weight and age for the subjects in the Final Dataset

Demographic Parameter	Healthy subjects			AD patients			Asthma patients			Total		
	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)
Age (year)	202	34.6 (11.5)	18.0 (32.0 – 63.0)	1839	37.9 (13.6)	18.0 (36.0 – 88.0)	2015	48.0 (14.7)	50.0 (12.0 – 83.0)	4056	42.7 (15.0)	43.0 (12.0 – 88.0)
Weight (kg)	202	76.0 (9.87)	77.3 (52.1 – 94.6)	1839	76.5 (18.4)	74.0 (39.8 – 175)	2015	80.0 (19.6)	78.0 (32.0 – 186)	4056	78.2 (18.8)	76.0 (32.0 – 186)
Weight of adolescents (≥12 to <18 year) (kg)	0	NA	NA	0	NA	NA	69	60.0 (18.2)	56.0 (32.0 – 122)	69	60.0 (18.2)	56.0 (32.0 – 122)
Weight of adults (≥18 year) (kg)	202	76.0 (9.87)	77.3 (52.1 – 94.6)	1839	76.5 (18.4)	74.0 (39.8 – 175)	1946	80.7 (19.3)	78.0 (39.0 – 186)	3987	78.5 (18.6)	76.2 (39.0 – 186)

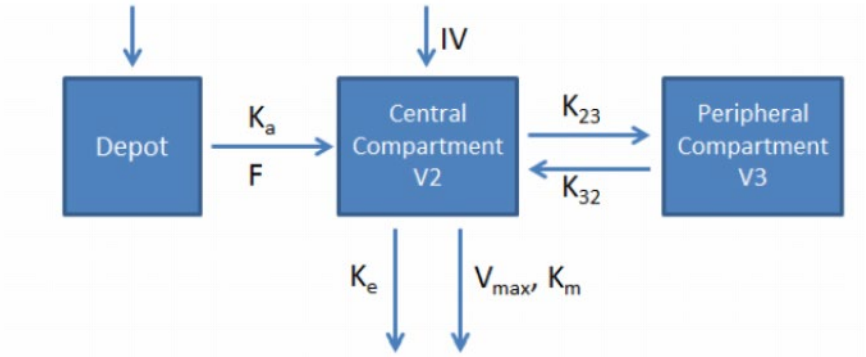
NA: notapplicable

The Pop PK analysis was performed with NONMEM (version 7.4) running on a LINUX cluster of multi-processor computers.

The base model structure of asthma Pop PK model (two-compartment model with first order absorption and parallel linear and nonlinear (Michaelis-Menten) elimination) was used as the starting point for the development of the global Pop PK base model. Two modelling approaches, one-step analysis (no parameter fixed at prior values) and step-wise analysis (fixing parameters

based on prior values), were evaluated for base model development. The final global Pop PK base model was selected on the basis of overall model performance (Figure 1).

Figure 1 - Schematic structure of dupilumab global population PK model (Study POH0668)



Abbreviation: F-bioavailability; k23, k32 – inter-compartmental rate constants; k_e – elimination rate constant; K_a – absorption rate constant; V_2 – central compartment volume; k_m – Michaelis constant; V_3 – peripheral compartment volume ; V_{max} – maximum target-mediated rate of elimination.

Base model selection

Parameter estimates from step-wise and one-step analyses were consistent with each other and with those from prior AD and asthma models, except for numerical differences on K_m. Both candidate base models well described AD and asthma data as evidenced by the lines of best fit through the data in the plots of observed versus individual predicted concentrations with little bias. Given both candidate global Pop PK base models performed similarly in describing dupilumab PK in AD and asthma patients, both models were further evaluated for the assessment of weight effects.

Parameter estimates of global Pop PK base model (without inclusion of weight effects)

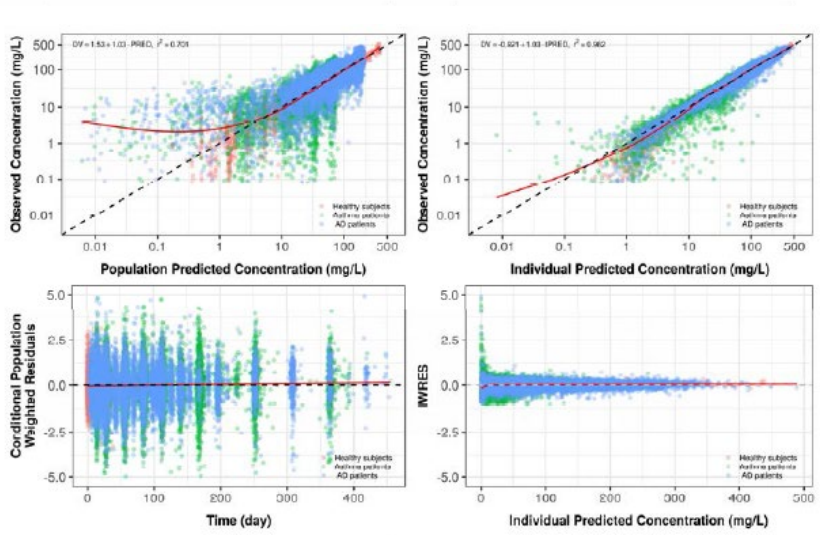
Parameter	Global Pop PK base model		Asthma Pop PK model[a]	AD Pop PK model[b]
	Step-wise	One-step	One-step	Step-wise
	Population Mean			
	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)	Estimate (SE)
K_e (1/day)	0.044 (0.81%)	0.041 (2.34%)	0.041 (2.23%)	0.045 (0.00049)[d]
V_2 (L)	3.10 (0.52%)	2.85 (3.67%)	2.70 (2.30%)	2.76 (0.021)[d]
K_{23} (1/day)	0.11 (6.05%)	0.10 (5.82%)	0.10 (4.91%)	0.21 (0.0286)[e]
K_{32} (1/day)	0.19 (8.25%)	0.16 (3.03%)	0.18 (4.45%)	0.31[e]
V_{max} (mg/L/day)	1.29 (1.49%)	1.49 (2.86%)	1.44 (0.57%)	1.07 (0.0162)[f]
K_m (mg/L)	0.74 (36.6%)	2.61 (8.42%)	2.29 (8.73%)	0.01 (Fixed)[e]
K_a (1/day)	0.23 (5.09%)	0.26 (2.92%)	0.26 (3.67%)	0.31 (0.0094)[f]
V_2 ~ WT[c]	--	--	0.84 (2.66%)	0.92 (0.027)[d]
	Inter-individual variability			
	[%CV (%RSE)]			[%CV (SE)]
K_e	27.6 (4.54%)	25.9 (4.95%)	19.3 (11.2%)	54.9 (0.0098)[d]
V_2	20.3 (5.07%)	14.3 (14.6%)	9.51 (17.4%)	46.5 (0.0065)[d]
V_{max}	32.2 (4.95%)	33.1 (4.42%)	25.9 (6.93%)	--
K_a	47.6 (13.0%)	40.7 (6.40%)	53.8 (7.80%)	--
F_1	51.8 (30.5%)	60.6 (10.1%)	35.8 (11.1%)	--
	Residual variability			
	[Estimate (%RSE)]			[%CV (SE)]
Proportional_residual term	0.16 (0.76%)	0.17 (0.64%)	0.20 (0.83%)	12.4 (0.18)[d]
Additive_residual term	2.93 (2.07%)	1.96 (2.18%)	2.86 (2.84%)	6.17 (0.23)[d]

a. Source document : asthma Pop PK report (POH0530)
b. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1)
c. Power coefficient between weight (WT) and PK parameter
d. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 3 (primary base model)
e. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 1; K_{32} was derived per equation as $k_{32} = k_{23}/M_{32}$, the mean (SE) of M_{32} estimate is 0.686 (0.00986)
f. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 2

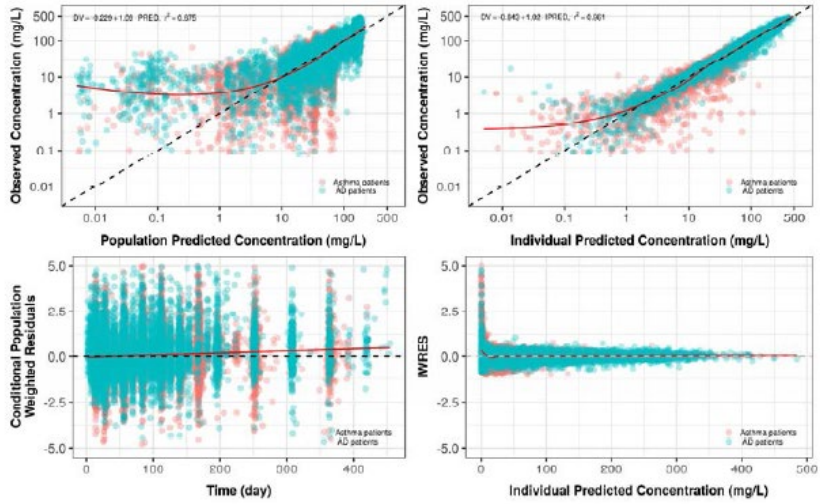
Abbreviation : K_e: linear elimination rate constant; V_2: volume of central compartment; K_{23}, K_{32}: inter-compartment distribution rate constants; V_{max}: maximum target-mediated rate of elimination; K_m: Michaelis constant; K_a: absorption rate constant; F_1: bioavailability; Vss: volume of distribution at steady-state; SE: standard error ; %RSE: Percentage of Relative Standard Error (100% * SE / Estimate)

Goodness-of-fit plots from global Pop PK base model (Without inclusion of weight effects)

A. One-step analysis



B. Step-wise analysis



<u>BODY WEIGHT EFFECTS ON PK</u>

The inclusion of weight effects into the global Pop PK base model during forward selection process including, presented in order of inclusion: 1) body weight on V2; 2) body weight on Vmax; 3) body weight on K_e.

After backward elimination, there was no exclusion of body weight effect on any of the above parameters in the model. This covariate analysis of weight effects finding was consistent with those from prior Pop PK model of AD (R668-MX-16103-CP-01v1) and asthma (POH0530).

Summary of weight effects assessment during forward selection and backward elimination

Inclusion of weight effects		Model from step-wise approach			Model from one-step approach		
		Selected covariate	MVOF	Change in MVOF from previous run	Selected covariate	MVOF	Change in MVOF from previous run
Base model		NA	165546.4	NA	NA	172974.9	NA
Forward selection	Round 1	WT_V_2	163273.4	-2273.0	WT_V_2	170786.4	-2188.5
	Round 2	WT_V_{max}	163150.9	-122.5	WT_V_{max}	170684.3	-102.1
	Round 3	WT_K_e	163123.7	-27.3	WT_K_e	170666.6	-17.7
Backward elimination		No covariate removed					

Abbreviation : WT : weight; V_2 : volume of central compartment; V_{max}: maximum target-mediated rate of elimination; K_e: linear elimination rate constant; MVOF : minimal value of objection function; NA : not available

After inclusion of weight effect, inter-individual variability (IIV) estimates for key PK parameters (i.e. Ke, V2 and Vmax) decreased approximately 4.0% – 6.21% compared to the base model.

Final global Pop PK base model

The majority of parameter estimates from global Pop PK models with either step-wise or one-step analysis approach, were mostly comparable. The precision of PK parameter estimates was high throughout (%RSE < 40%). Key PK parameter estimates (e.g. bioavailability (F1), distribution volume at steady-state (Vss), linear clearance (CL)) based upon one-step analysis were more consistent with those of prior AD and asthma Pop PK models. The performance of global Pop PK model with step-wise or one-step analysis approach was further evaluated by goodness-of-fit plots.

The global Pop PK base model with one-step analysis approach performed slightly better than the model with step-wise approach, as evidenced by relative lower r2 for both population and individual fits. Therefore, one-step analysis was selected for the final model based on the consistency of parameter estimates with prior AD and asthma models as well as the improved goodness-of-fit diagnostic plots. In the final global Pop PK model, the magnitude of unexplained IIV was moderate for K_a (44.0% CV), F1 (41.9% CV), and V_{max} (29.1% CV), and relatively small for K_e (21.7% CV) and V2 (8.09% CV). Consistent with prior AD and asthma models, weight showed to have a notable effect explaining between-subject variability of dupilumab PK for both AD and asthma patients as shown in final global Pop PK base model. After inclusion of weight effects, IIV estimates for key PK parameters (i.e. K_e, V_2 and V_{max}) decreased approximately 4.0% – 6.21% compared to the base model.

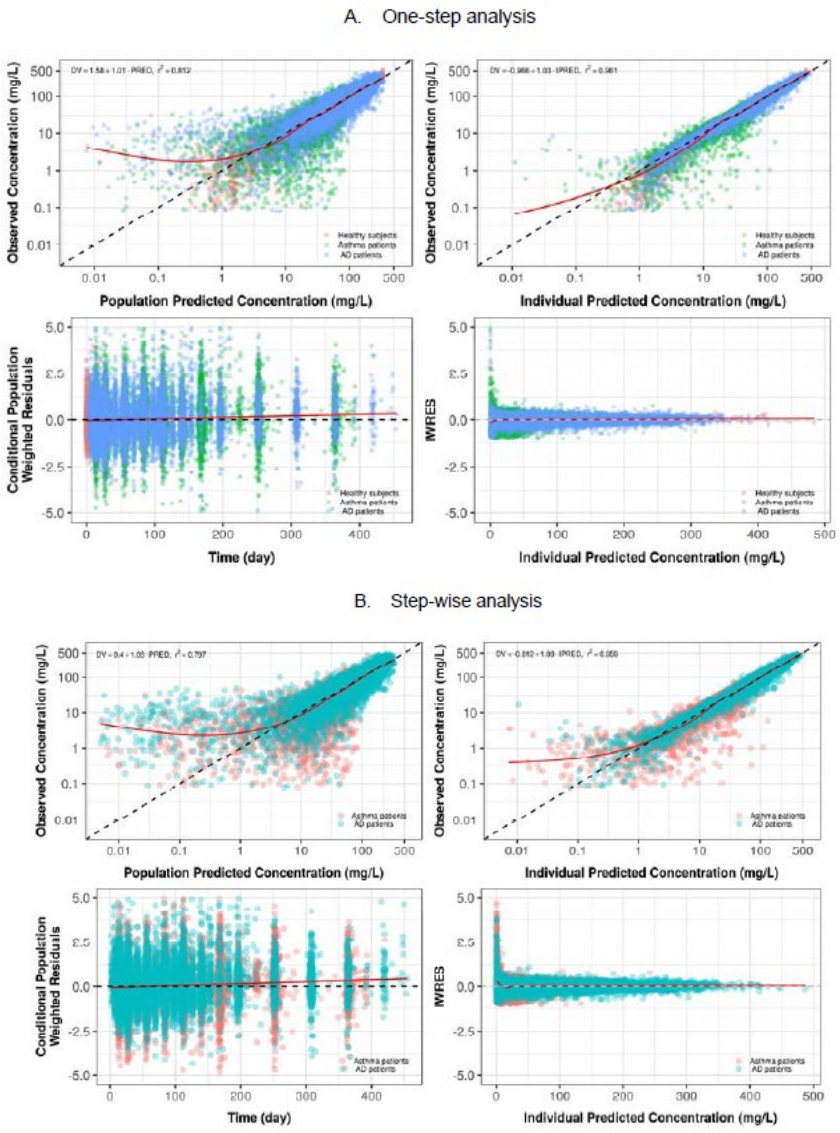
Parameter estimates of final global Pop PK base model (inclusion of weight effects)

Parameter	Global Pop PK base model		Asthma Pop PK model[a]	AD Pop PK model[b]
	Step-wise	One-step	One-step	Step-wise
	Population Mean			
	Estimate (% RSE)	Estimate (% RSE)	Estimate (% RSE)	Estimate (SE)
K_e (1/day)	0.044 (0.74%)	0.041 (2.21%)	0.042 (2.77%)	0.048 (0.00078)[d]
V_2 (L)	3.07 (0.39%)	2.79 (1.98%)	2.76 (2.43%)	2.74 (0.021)[d]
K_{23} (1/day)	0.11 (6.05%)	0.089 (5.66%)	0.10 (6.97%)	0.21 (0.0286)[e]
K_{32} (1/day)	0.19 (8.25%)	0.15 (2.89%)	0.16 (4.36%)	0.31[e]
V_{max} (mg/L/day)	1.29 (1.05%)	1.48 (2.67%)	1.39 (3.80%)	1.07 (0.0162)[f]
K_m (mg/L)	0.75 (36.6%)	2.52 (8.41%)	2.08 (13.6%)	0.01 (Fixed)[e]
K_a (1/day)	0.23 (5.09%)	0.25 (2.75%)	0.26 (3.80%)	0.31 (0.0094)[f]
F_1 (%)	69.5 (5.31%)	62.8 (2.99%)	60.9 (3.27%)	64.2 (0.0091)[e]
CL (L/day)	0.135	0.114	0.116	0.131
V_{ss} (L)	4.85	4.46	4.37	4.60
V_2 ~ WT[c]	0.73 (2.10%)	0.72 (2.28%)	0.67 (3.89%)	0.82 (0.031)[d]
K_e ~ WT[c]	0.17 (17.5%)	0.12 (26.0%)	0.22 (12.1%)	--
K_e ~ BMI	--	--	--	0.37 (0.053)[d]
V_{max} ~ WT[c]	0.32 (12.4%)	0.33 (13.0%)	0.22 (24.0%)	--
	Inter-individual variability			
		[%CV (%RSE)]		[%CV (SE)]
K_e	22.8 (4.47%)	21.7 (5.06%)	19.6 (10.6%)	54.1 (0.01)[d]
V_2	7.26 (14.9%)	8.09 (16.1%)	9.13 (18.2%)	45.4 (0.0068)[d]
V_{max}	28.0 (4.50%)	29.1 (4.38%)	24.3 (7.69%)	--
K_a	47.6 (13.0%)	44.0 (5.95%)	49.2 (7.68%)	--
F_1	51.8 (30.5%)	41.9 (7.82%)	36.3 (11.9%)	--
	Residual variability			
		[%CV (%RSE)]		[%CV (SE)]
Proportional_residual term	0.32 (12.4%)	0.17 (0.63%)	0.20 (0.88%)	12.5 (0.18)[d]
Additive_residual term	0.32 (12.4%)	2.06 (2.05%)	1.73 (2.86%)	6.06 (0.23)[d]

a. Source document : asthma Pop PK report (POH0530)
b. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1)
c. Power coefficient between weight (WT) and PK parameter
d. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 4 (primary covariate model)
e. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 1; K_{32} was derived per equation as $k_{32} = k_{23}/M_{32}$, the mean (SE) of M_{32} estimate is 0.686 (0.00986)
f. Source document : AD Pop PK report (REGN668-MX-16103-CP-01V1), Model 2

Abbreviation : K_e: linear elimination rate constant; V_2: volume of central compartment; K_{23}, K_{32}: inter-compartment distribution rate constants; V_{max}: maximum target-mediated rate of elimination; K_m: Michaelis constant; K_a: absorption rate constant; F_1: bioavailability; CL : linear clearance; Vss: volume of distribution at steady-state; SE : standard error ; %RSE: Percentage of Relative Standard Error (100% * SE / Estimate)

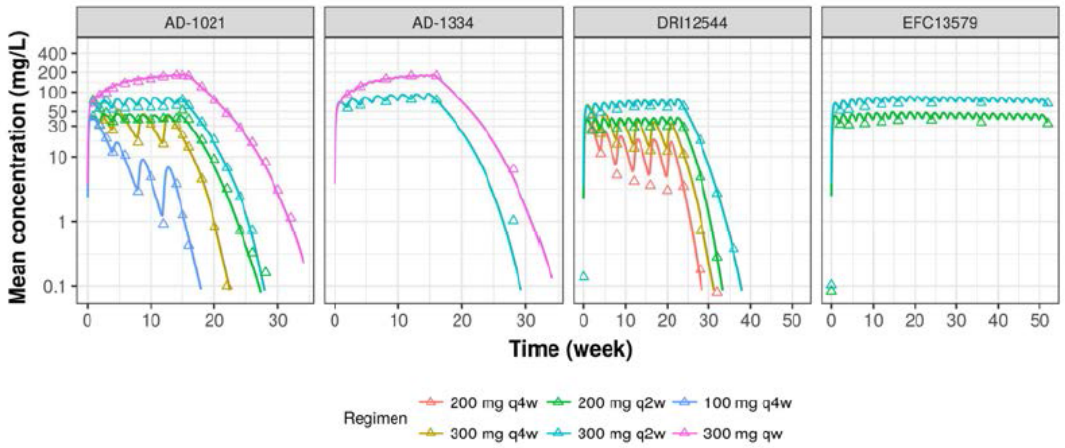
Goodness-of-fit plots from final global Pop PK base model



MODEL VALIDATION

To validate the predictability of final model, model simulations was compared to the observed mean PK profiles from representative AD and asthma studies (i.e. a dose ranging study as well as a pivotal Phase 3 study for each indication). The simulations based upon the global base model well described the observed PK profiles in AD and asthma patients across a wide dose range (100 mg q4w to 300 mg qw).

Observed vs. simulated mean concentration-time profiles from representative AD and asthma studies



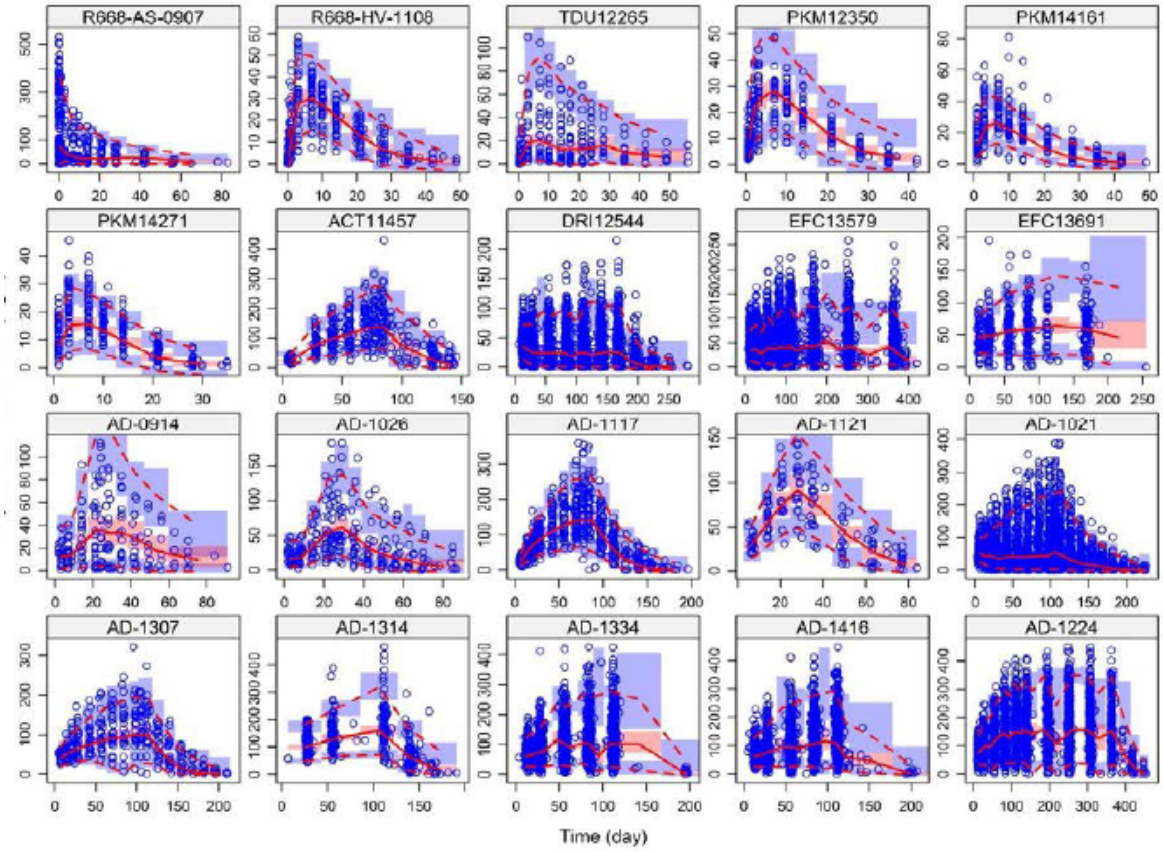
Note : triangle indicate observed mean concentration at each time point; solid line represents simulated mean PK profile for each regimen; Study AD-1021 and AD-1334 are Phase 2b dose ranging study and Phase 3 pivotal study (SOLO1) from AD patients, respectively; studies DRI12544 and EFC13579 are Phase 2b dose ranging study and Phase 3 pivotal study (Quest) from asthma patients; respectively.

The simulations based upon the global base model well described the observed PK profiles in AD and asthma patients across a wide dose range (100 mg q4w to 300 mg qw). Overall, a good agreement between the model-predicted and observed PK profiles supports the predictability of final global Pop PK model (one-step analysis) for TH2 inflammatory disease populations across a wide dose range.

The robustness of the final model and the accuracy of parameter estimates were assessed using a bootstrap method. From the Final Dataset of 4056 subjects, 500 runs were launched. 431 successful runs were obtained with a successful covariance step (86.2% of the total number of runs launched). For each run, Pop PK parameters were estimated and the corresponding descriptive statistics such as median, 2.5th and 97.5th percentiles were computed for each Pop PK parameters. The median values obtained from the bootstrap were compared to those obtained in the final model of the original dataset.

The visual predictive checks (VPC) technique was used to evaluate the performance of the final global Pop PK model (one-step analysis approach). The results of the VPC showed that a large majority of the observed concentrations were within in the prediction range [5th-95th percentiles] and a few concentration points outside of the percentile range appeared to distribute evenly on either side.

Visual predictive checks for final global Pop PK base model by study



Note: Legend: blue dots: observations; solid red line: median; solid dashed lines: 5th and 95th percentiles; pink and light blue areas: confidence intervals of median and centiles.

To assess the influence of outlier exclusion, the final model was performed on the Final Dataset including outlier samples. It was observed that there were no major changes in parameter estimates with or without the inclusion of outliers.

c) POH0687

Empirical Exposure-Response Analysis of Nasal Polyps Score, Nasal Congestion, Loss of Sense of Smell and 22-Item Sino-nasal Outcome Test for Dupilumab Nasal Polyposis Phase 3 Studies

The two pivotal Phase 3 studies EFC14146 and EFC14280 were included in the PK/PD analyses

Table 1 - List of Phase 3 CRSwNP studies

Study number/ Status at submission cutoff	Study objective	Treatment/ follow-up duration	Patients randomized/ treated[a]
EFC14146 Completed	To evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of MFNS in reducing nasal congestion/obstruction severity and endoscopic NPS in adult patients with bilateral NP. (Co-primary endpoints: 1) Change from baseline in the nasal congestion/obstruction score at Week 24, 2) Change from baseline in the NPS at Week 24, and 3) Japan only: Change from baseline in Lund-Mackay score at week 24)	24/24 weeks	Randomized/treated=276/275 (Pbo:133: dupilumab 300 mg q2w: 142 as treated)
EFC14280 Primary analysis completed[c]	To evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of MFNS in reducing nasal congestion/obstruction severity and endoscopic NPS in adult patients with bilateral NP. (Co-primary endpoints: 1) Change from baseline in the nasal congestion/obstruction score at Week 24, 2) Change from baseline in the NPS at Week 24, and 3) Japan only: Change from baseline in Lund-Mackay score at week 24)	52/12 weeks	Randomized/treated=448/447 (Pbo: 152; 300 mg q2w [Arm A]: 150 300 mg q2w-q4w [Arm B]: 145 as treated)[b]

MFNS=mometasone furoate nasal spray; NP=nasal polyposis, NPS=nasal polyp score, Pbo=placebo, q2w=every 2 weeks, q4w=every 4 weeks, SC=subcutaneous;

a Including all data up to the clinical database cutoff date (Aug 29, 2018)

b Patients in Arm A received dupilumab 300 mg q2w for 52 weeks and patients in Arm B received dupilumab q2w for 24 weeks followed by dupilumab 300 mg q4w until Week 52.

c Treatment period for EFC14280 is completed, 12-week follow-up is still ongoing.

For the E-R analysis, co-primary endpoints of nasal polyps score (NPS) and nasal congestion/obstruction (NC), secondary endpoints of decreased/loss of sense of smell (LOSS) and 22-item sino-nasal outcome test score (SNOT-22) were used. For each efficacy endpoint, two time points were considered, change from baseline to Week 24, and change from baseline to Week 52. Studies EFC14146 and EFC14280 were pooled together to evaluate the exposure-response relationship for the four endpoints at Week 24 while Study EFC14280 alone was used to examine the exposure response relationship for the four endpoints at Week 52.

Missing data for these efficacy endpoints were imputed, based on the worst observation carried forward (WOCF) method for patients who underwent surgery for NP or received rescue medicine. This imputation is consistent with the missing data imputation strategy specified in the integrated summary of efficacy (ISE) report. For patients who discontinued treatment without being rescued by surgery or rescue medicine, the multiple imputation method was used. However, due to lack of an appropriate method to integrate the multiple imputation method in the E-R modelling with the variable selection procedures, patients who discontinued treatment without being rescued by surgery or rescue medicine were excluded from the E-R analysis. Therefore, the PK/PD analysis population may not match the efficacy population in the clinical study report in the two studies.

At Week 52, Study EFC14280 had the PK data cut-off as 6 August 2018, about 70% data at Week 52 observed Ctrough were available and so missing observed Ctrough at Week 52 was predicted using the relevant post hoc population PK estimate (Study POH0611).

Base model selection

Three base models of the E-R relationship, linear, log linear and maximum drug induced effect (Emax), with appropriate covariates, were compared to select the best model by a goodness of fit criterion (the Akaike information criterion with sample size correction).

For the base PK/PD model, the main effects (placebo effect) in the model include the baseline score of the efficacy endpoint, study identifier, asthma/ NSAID (nonsteroidal anti-inflammatory drug)

exacerbated respiratory disease (NERD) status (Yes vs. No), Prior NP surgery (Yes vs No) and region (Asia, Latin America, east Europe, and Western countries).

Additional covariate selection

Effects of the following additional baseline covariates, either as a main effect or an interaction effect with dupilumab concentration, were explored in the PK/PD model:

- Age (year)
- Gender (male/female)
- Race (Caucasian/white, American Indian or Alaska native, Black, Asian/Oriental, multiple, native Hawaiian or other Pacific Islander, other)
- Region (Asia, Latin America, East Europe, Western)
- Territory (European Union, North America, Asia)
- Ethnicity (Hispanic, non-Hispanic)
- Weight (kg)
- Body mass index (BMI, kg/m2)
- Asthma history (Yes, No)
- NSAID exacerbated respiratory disease (NERD) history (Yes, No)
- Allergic rhinitis history (Yes, No)
- Past 2 year systemic corticosteroids (SCS) history (Yes, No)
- University of Pennsylvania smell identification test (UPSIT)
- Anti-drug antibody (ADA) (All negative, Pre-existing, Treatment-emergent)

Baseline blood biomarkers including eosinophil (EOS), Immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC) and periostin.

Final model evaluation

To examine the validity of the PK/PD model, model predictions and observed effects were compared. The observed effects for each dose were estimated using the Analysis of covariance (ANCOVA) method for each study separately. The ANCOVA model included the change score from baseline at Week 24 as the response variable and treatment (as treated), the baseline score, asthma/NERD status (Yes vs. No), Prior NP surgery (Yes vs No) and region (Asia, Latin America, east Europe, and Western countries) as covariates.

Sensitivity analyses

In Study EFC14280, approximately 6% patients who discontinued treatment without being rescued by surgery or rescue medicine were excluded from the E-R analysis at Week 52.

Sensitivity analyses were conducted by further excluding discontinued patients who underwent surgery for NP or received rescue medicine (approximately 7% patients) at Week 52 (Table 2).

Sensitivity analyses were also conducted for completers at Week 52. In the completer analyses, patient with missing observed Ctrough or discontinued treatment at Week 52 were excluded (Table 2).

Table 2 - Analysis population in the sensitivity analyses

Analysis (Study EFC14280 at Week 52)	Treatment Group: n*	Patient Population
Full dataset of E-R analysis	Placebo: 141 300 mg q2w [Arm A]: 140 300 mg q2w-q4w [Arm B]: 138	Discontinued patients without being rescued by surgery or rescue medicine were excluded from the E-R analysis
Sensitivity analyses excluding discontinued patients underwent surgery for NP or received rescue medicine	Placebo: 119 300 mg q2w [Arm A]: 131 300 mg q2w-q4w [Arm B]: 136	Discontinued patients who underwent surgery for NP or received rescue medicine were further excluded. (i.e. Patients who completed 52-week treatment)
Sensitivity analyses of completers	Placebo: 119 300 mg q2w [Arm A]: 93 300 mg q2w-q4w [Arm B]: 98	Patients who completed 52-week treatment and had observed C_{trough}

*Number of patients (n) was calculated based on NPS endpoint; n for other endpoints is similar to that for NPS endpoint.

RESULTS

NPS

Quartile Plot and Summary Table at Week 24

The NPS response for 300 mg q2w dose regimen at Week 24 appeared to be generally similar over the 3 higher exposure quartiles, suggesting that a further increase in dose/exposure would not result in a better response.

Figure 1 - Scatter Plot of NPS Change from Baseline against Observed C_{trough} (mg/L) at Week 24 (Studies EFC14146 and EFC14280)

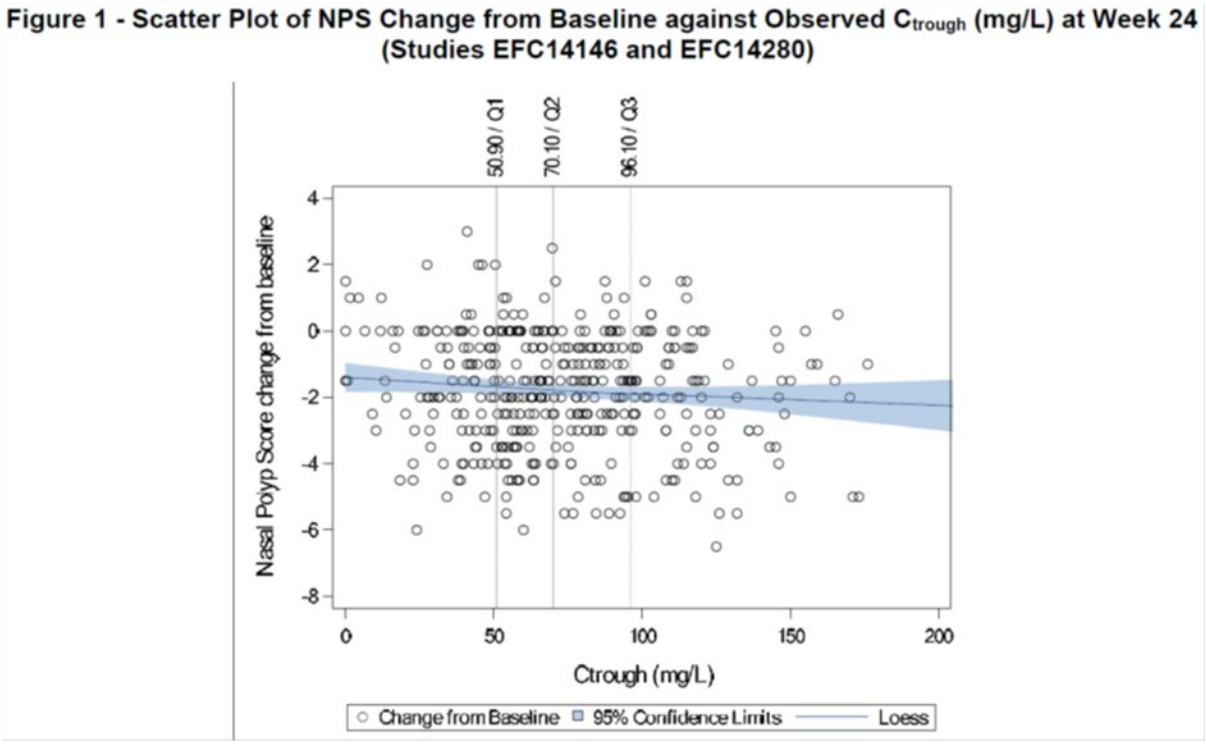


Table 3 - Summary of Nasal Polyps Score Change from Baseline by Observed C_{trough} (mg/L) Quartile at Week 24 (Studies EFC14146 and EFC14280)

Quartile	Number of patients	NPS Change Mean	NPS Change Range	NPS Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error
1	103	-1.490	(-6.000,3.000)	0.177	33.63	(0.04,50.90)	1.40
2	103	-1.883	(-6.000,2.500)	0.172	60.16	(51.20,70.10)	0.53
3	102	-1.873	(-5.500,1.500)	0.165	83.57	(70.40,96.10)	0.72
4	102	-1.926	(-6.500,4.500)	0.187	123.1	(96.40,208.0)	2.38

Quartile values: Q1= 50.9; Q2= 70.1; Q3= 96.1 mg/L

The NPS response for 300 mg q2w dose regimen at Week 24 appeared to be generally similar over the 3 higher exposure quartiles, suggesting that a further increase in dose/exposure would not result in a better response.

Exposure-Response Model at Week 24

An Emax model is selected as the base model. The EC50 was stably estimated but with a large confidence interval, which reflected the high variability of responses at the low concentration range. Higher baseline age or higher UPSIT score was associated with significantly decreased placebo-adjusted treatment effect at Week 24 (significantly increased mean change score) given a fixed Ctrough while higher baseline periostin was associated with significantly increased placebo-adjusted treatment effect at Week 24.

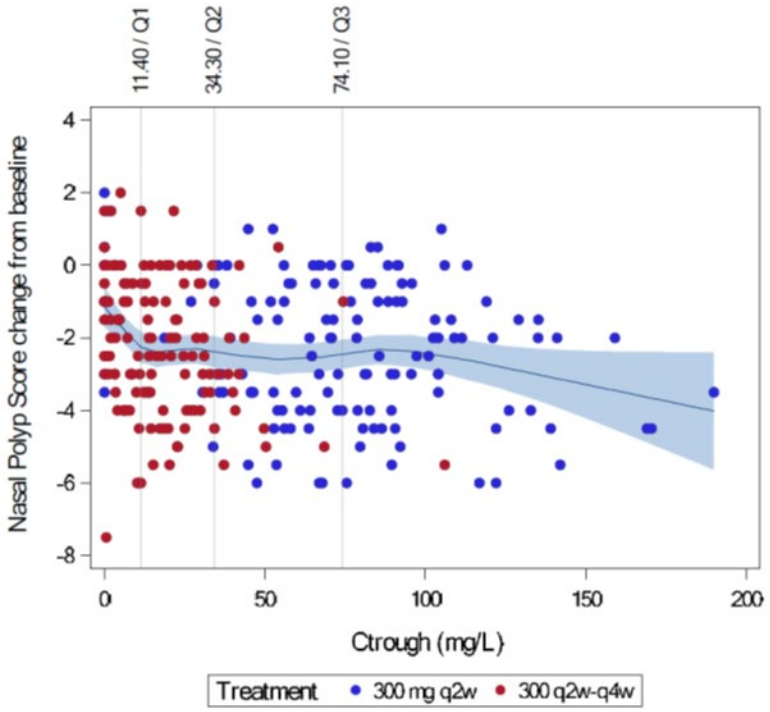
Nasal Polyps Score Change from Baseline vs. Ctrough at Week 24: the PK/PD Model Parameter Estimations (Studies EFC14146 and EFC14280)

Parameter	Estimate	95% CI	Standard Error	P-value
b0	2.308	1.659 , 2.958	0.331	<.0001
b1: baseline Nasal Polyps	-0.326	-0.416 , -0.237	0.046	<.0001
b2: Study=EFC14146	-0.240	-0.525 , 0.044	0.145	0.0973
b3: Asia vs Western	-0.021	-0.471 , 0.429	0.229	0.9259
b4: Latin America vs Western	0.254	-0.067 , 0.574	0.163	0.1203
b5: East Europe vs Western	0.277	-0.013 , 0.566	0.147	0.0610
b6: asthma/NERD status=Y	-0.168	-0.404 , 0.069	0.121	0.1651
b7: Prior NP surgery=Y	-0.220	-0.465 , 0.026	0.125	0.0790
b8: Baseline age-median base age	-0.008	-0.021 , 0.005	0.007	0.2378
b9: Baseline UPSIT/100-median base UPSIT/100	-2.847	-4.948 , -0.746	1.070	0.0080
b10: Baseline log(periostin) - median(baseline log(periostin))	0.052	-0.385 , 0.49	0.223	0.8138
Emax0	-2.133	-2.492 , -1.773	0.183	<.0001
Emax1: Baseline age-median base age	0.043	0.023 , 0.062	0.010	<.0001
Emax2: Baseline UPSIT/100-median base UPSIT/100	4.217	1.249 , 7.184	1.511	0.0054
Emax3: Baseline log(peri) - median(baseline log(peri))	-0.865	-1.453 , -0.277	0.300	0.0040
EC_{50}#	3.843	-4.773 , 12.46	4.388	0.3815
sigma**2	1.981	1.769 , 2.192	0.108	<.0001

#EC_{50} with unit mg/L was estimated with wide 95% CI covering 0.

Quartile Plot and Summary Table at Week 52

Figure 3 - Scatter Plot of NPS Change from Baseline against C_{trough} (mg/L) at Week 52 (Study EFC14280)



The majority of patients in the 300 mg q2w-q4w regimen were in the lower 2 quartiles (Q1 and Q2) while the majority of patients in the 300 mg q2w dose regimen were in the upper 2 quartiles (Q3 and Q4) at Week 52. At the lowest quartile of exposure, comprising mostly of patients at 300 mg q2w-q4w, there was a numerically smaller improvement in NPS than at the other three quartiles suggesting greater efficacy at Week 52 (in terms of maximum treatment effect) with 300 mg q2w dupilumab.

Table 6 - Summary of NPS Change from Baseline by C_{trough} (mg/L) Quartile at Week 52 (Study EFC14280)

Quartile	Number of patients	NPS Change Mean	NPS Change Range	NPS Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error	Number of patients: 300 mg q2w:300 mg q2w-q4w
1	70	-1.671	(-7.500,2.000)	0.240	3.86	(0.04,11.40)	0.45	10:60
2	70	-2.271	(-5.500,1.500)	0.210	22.59	(12.10,34.30)	0.83	7:63
3	69	-2.601	(-6.000,1.000)	0.235	53.84	(34.78,74.10)	1.48	56:13
4	69	-2.471	(-6.000,1.000)	0.224	103.1	(74.40,189.9)	3.02	67:2

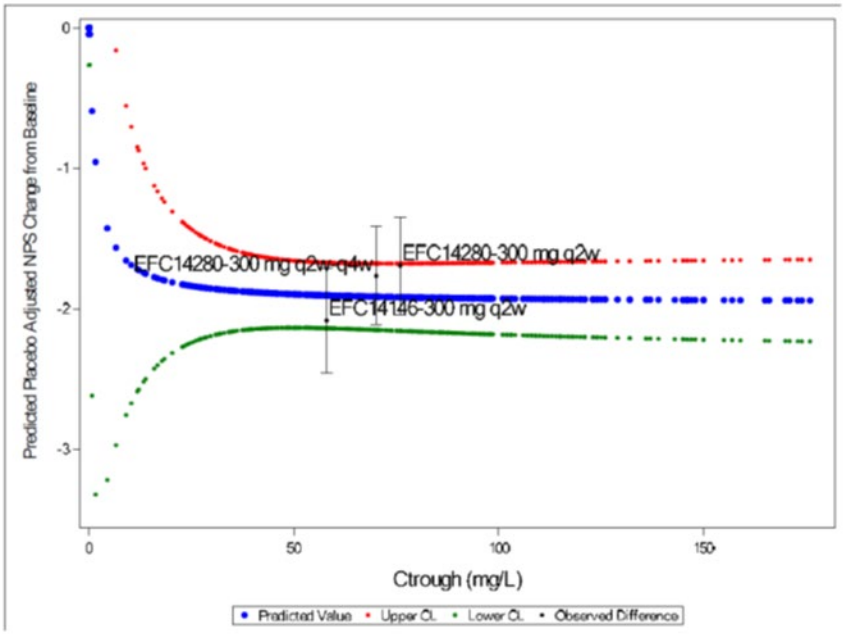
Quartile values: Q1= 11.4; Q2= 34.3; Q3= 74.1 mg/L

Exposure-Response Model at Week 52

The EC50 was stably estimated but with a large confidence interval, which reflected the high variability of responses at the low concentration range. Higher baseline age or higher baseline BMI associated with significantly decreased placebo-adjusted treatment effect at Week 52 (significantly

increased mean change score) given a fixed Ctrough while a prior medical history of asthma/NERD associated with significantly increased placebo-adjusted treatment effect at Week 52.

Figure 2 - PK/PD Model Predicted Exposure-response Curve Overlaid with Observed* Placebo-adjusted Mean NPS Change Score from Baseline at Week 24 (Studies EFC14146 and EFC14280)



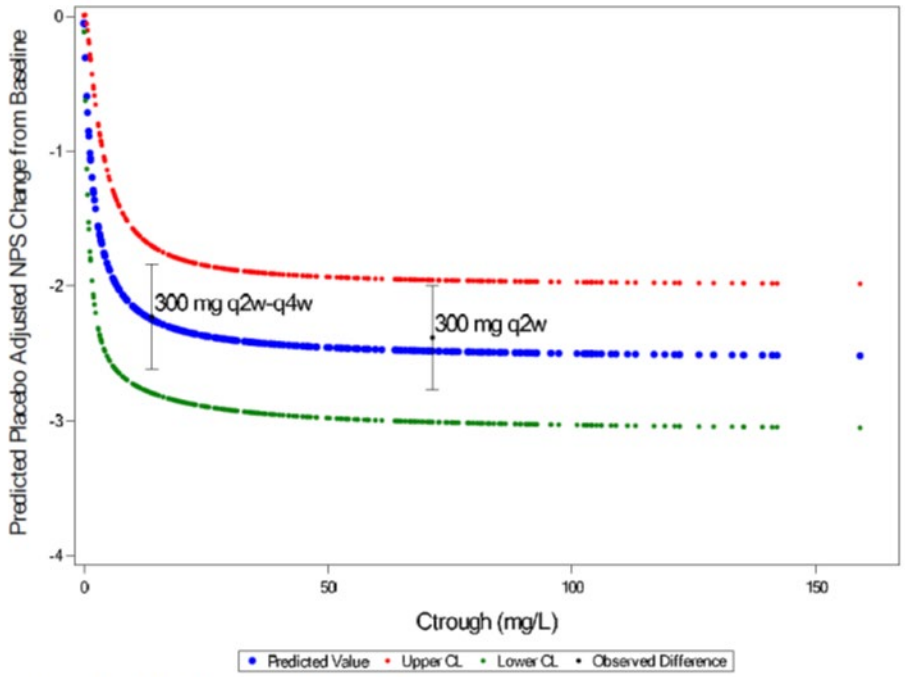
*Observed effects were based on ANCOVA analysis of observed data.

Nasal Polyps Score Change from Baseline vs. Ctrough (mg/L) at Week 52: the PK/PD Model Parameter Estimations (Study EFC14280)

Parameter	Estimate	95% CI	Standard Error	P-value
b0	1.889	1.025 , 2.753	0.440	<.0001
b1: Baseline Nasal Polyps Score	-0.324	-0.447 , -0.202	0.062	<.0001
b2: Asia vs Western	0.023	-0.47 , 0.515	0.251	0.9275
b3: Latin America vs Western	0.534	0.172 , 0.897	0.184	0.0039
b4: East Europe vs Western	0.362	-0.156 , 0.881	0.264	0.1701
b5: asthma/NERD status=Y	0.241	-0.243 , 0.726	0.247	0.3285
b6: Prior NP surgery=Y	-0.437	-0.768 , -0.106	0.168	0.0097
b7: Baseline age-median baseline age	-0.015	-0.034 , 0.004	0.010	0.1273
b8: Baseline bmi-median baseline bmi	-0.038	-0.081 , 0.004	0.022	0.0759
Emax0	-2.080	-2.617 , -1.544	0.273	<.0001
Emax1: asthma/NERD status=Y	-0.761	-1.431 , -0.091	0.341	0.0261
Emax2: Baseline age-median baseline age	0.060	0.033 , 0.088	0.014	<.0001
Emax3: Baseline bmi-median baseline bmi	0.086	0.024 , 0.147	0.031	0.0063
EC_{50} (mg/L) #	1.749	-0.455 , 3.953	1.121	0.1195
sigma**2	2.281	1.97 , 2.591	0.158	<.0001

#EC_{50} with unit mg/L was estimated with wide 95% CI covering 0.

Figure 6 - PK/PD Model Predicted Exposure-response Curve Overlaid with Observed* Placebo-adjusted Mean NPS Change Score from Baseline at Week 52 (Study EFC14280)



*Observed effects were based on ANCOVA analysis of observed data.

Table 5 - Nasal Polyps Score Change from Baseline ANCOVA Model Estimate and PKPD Model Predicted Treatment Difference from Placebo at Week 24 (Studies EFC14146 and EFC14280)

Comparison vs Placebo	LS Mean Difference (95% CI) from ANCOVA Model[1]	Predicted Mean Difference (95% CI) from PK/PD Model[2]	Median C_{trough} at Week 24
EFC14146-300 mg q2w	-2.084 (-2.457 , -1.712)	-1.905 (-2.166 , -1.664)	57.60
EFC14280-300 mg q2w	-1.694 (-2.043 , -1.346)	-1.918 (-2.161 , -1.671)	76.00
EFC14280-300 mg q2w-q4w	-1.766 (-2.115 , -1.417)	-1.915 (-2.163 , -1.669)	70.25

[1] Least square means (95% CI) from ANCOVA model

[2] Predicted mean (95% CI) at median E_{max} and median C_{trough}

The PK/PD model prediction of NPS indicated that the treatment effect approached, but did not reach, the Emax at the exposure of 300 mg q2w-q4w and reached a plateau at the exposure of 300 mg q2w. These results are in line with a numerically greater improvement in NPS observed for 300 mg q2w compared to 300 mg q2w-q4w at Week 52.

NC

Quartile Plot and Summary Table at Week 24

The NC response over the higher exposure quartiles appeared to be generally similar.

Scatter Plot of Nasal Congestion Change from Baseline against Observed Ctrough (mg/L) at Week 24 (Studies EFC14146 and EFC14280)

Figure 7 - Scatter Plot of Nasal Congestion Change from Baseline against Observed C_{trough} (mg/L) at Week 24 (Studies EFC14146 and EFC14280)

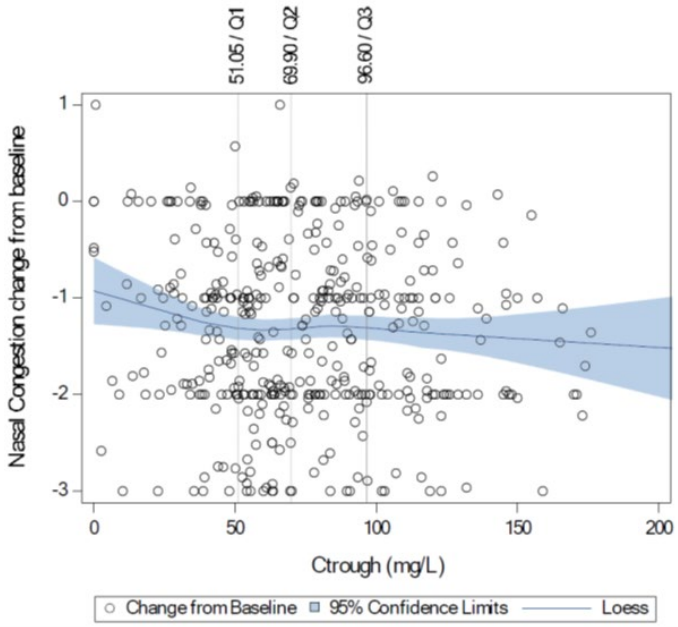


Table 11 - Summary of Nasal Congestion Change from Baseline by Observed C_{trough} (mg/L) Quartile at Week 24 (Studies EFC14146 and EFC14280)

Quartile	Number of patients	NC Change Mean	NC Change Range	NC Change Standard Error	C_{trough} Mean (mg/L)	C_{trough} Range (mg/L)	C_{trough} Standard Error
1	105	-1.198	(-3.000,1.000)	0.087	34.01	(0.04,50.90)	1.38
2	105	-1.409	(-3.000,1.000)	0.096	60.22	(51.20,69.70)	0.52
3	106	-1.243	(-3.000,0.214)	0.084	83.61	(70.10,96.60)	0.74
4	104	-1.380	(-3.000,0.259)	0.083	123.5	(96.90,208.0)	2.30

Quartile values: Q1= 51.05; Q2= 69.9; Q3= 96.6 mg/L

Figure 9 - Scatter Plot of NC Change from Baseline against C_{trough} (mg/L) at Week 52 (Study EFC14280)

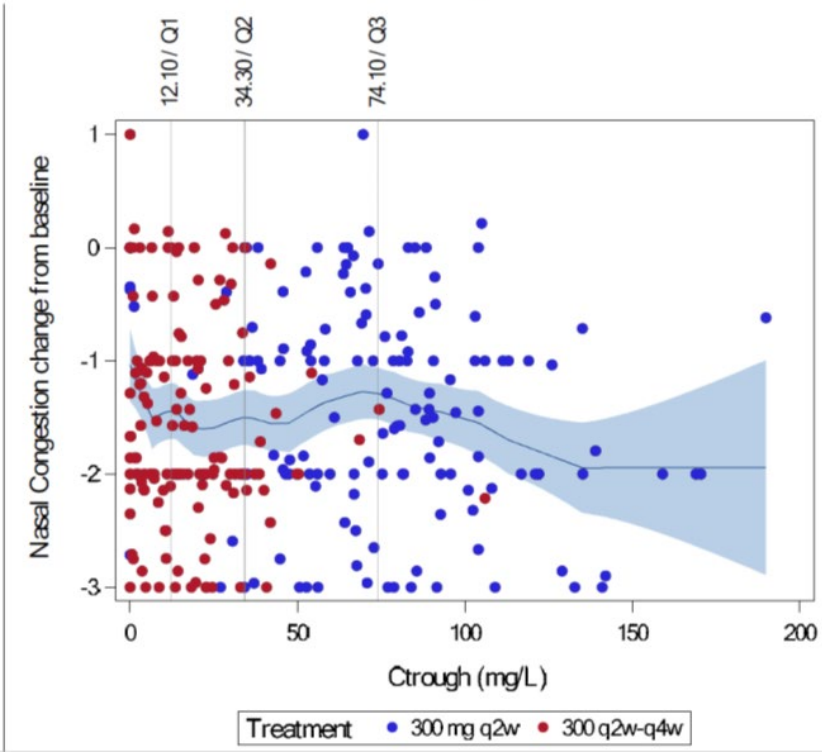


Table 14 - Summary of NC Change from Baseline by C_{trough} (mg/L) Quartile at Week 52 (Study EFC14280)

Quartile	Number of patients	NC Change Mean	NC Change Range	NC Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error	Number of patients: 300 mg q2w:300 mg q2w-q4w
1	72	-1.303	(-3.000,1.000)	0.119	3.98	(0.04,12.10)	0.46	9:63
2	72	-1.518	(-3.000,0.125)	0.113	22.67	(12.30,34.30)	0.83	8:64
3	72	-1.370	(-3.000,1.000)	0.115	53.68	(34.78,74.10)	1.45	58:14
4	71	-1.585	(-3.000,0.214)	0.101	102.4	(74.40,189.9)	2.97	69:2

Quartile values: Q1= 12.1; Q2= 34.3; Q3= 74.1 mg/L

Exposure-Response Model at Week 24

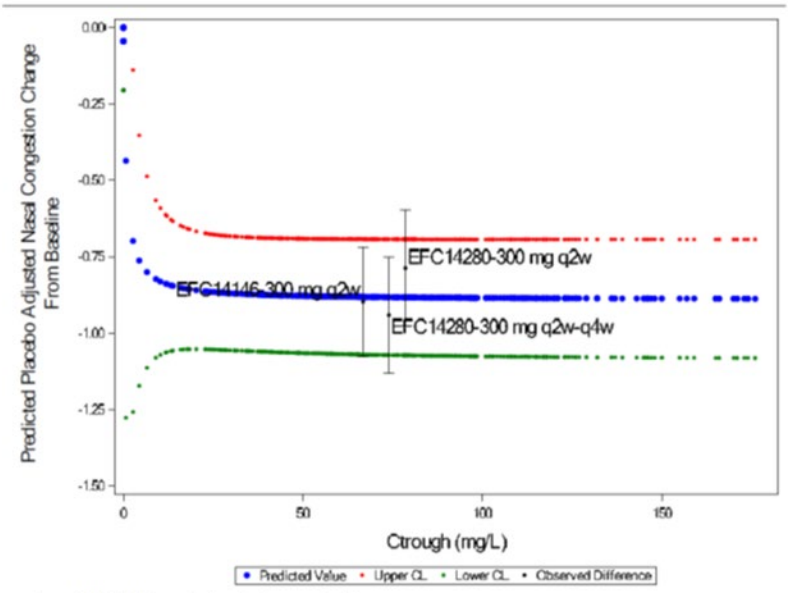
An Emax model was selected as the best base model. The EC50 was stably estimated but with a large confidence interval, which reflected the data variability. Higher baseline EOS or a prior history of asthma were each associated with significantly increased placebo-adjusted treatment effect at Week 24 (significantly decreased mean change score) given a fixed Ctrough at Week 24.

Nasal Congestion Change from Baseline vs. Ctrough at Week 24: the PK/PD Model Parameter Estimations (Studies EFC14146 and EFC14280)

Parameter	Estimate	95% CI	Standard Error	P-value
b0	0.860	0.552 , 1.167	0.157	<.0001
b1: baseline Nasal Congestion	-0.527	-0.629 , -0.426	0.052	<.0001
b2: Study=EFC14146	-0.105	-0.255 , 0.045	0.076	0.1691
b3: Asia vs Western	-0.060	-0.3 , 0.18	0.122	0.6253
b4: Latin America vs Western	0.040	-0.13 , 0.21	0.087	0.6471
b5: East Europe vs Western	-0.091	-0.244 , 0.062	0.078	0.2455
b6: asthma/NERD status=Yes	0.019	-0.31 , 0.348	0.168	0.9103
b7: Prior NP surgery=Yes	-0.043	-0.173 , 0.088	0.067	0.5221
b8: ln(Base EOS)-median ln(Base EOS)	0.025	-0.095 , 0.145	0.061	0.6806
b9: Asthma history=Yes	0.107	-0.244 , 0.457	0.178	0.5503
Emax0	-0.753	-0.952 , -0.554	0.101	<.0001
Emax1:ln(Base EOS)-median ln(Base EOS)	-0.199	-0.359 , -0.04	0.081	0.0141
Emax2:Asthma history=Yes	-0.299	-0.551 , -0.047	0.128	0.0199
EC_{50} (mg/L) #	0.747	-2.155 , 3.65	1.478	0.6133
sigma**2	0.587	0.525 , 0.648	0.031	<.0001

#EC_{50} with unit mg/L was estimated with wide 95% CI covering 0.

Figure 8 - PK/PD Model Predicted Exposure-response Curve Overlaid with Observed* Placebo-adjusted Mean NC Change Score from Baseline at Week 24 (Studies EFC14146 and EFC14280)



*Observed effects were based on ANCOVA analysis of observed data.

Table 13 - Nasal Congestion Change from Baseline ANCOVA Model Estimate and PKPD Model Predicted Treatment Difference from Placebo at Week 24 (Studies EFC14146 and EFC14280)

Comparison vs Placebo	LS Mean Difference (95% CI) from ANCOVA Model[1]	Predicted Mean Difference (95% CI) from PK/PD Model[2]	Median C_{trough} at Week 24
EFC14146-300 mg q2w	-0.898 (-1.077 , -0.718)	-0.88 (-1.069 , -0.692)	58.60
EFC14280-300 mg q2w	-0.787 (-0.977 , -0.597)	-0.883 (-1.072 , -0.693)	75.95
EFC14280-300 mg q2w-q4w	-0.941 (-1.13 , -0.752)	-0.882 (-1.071 , -0.693)	70.10

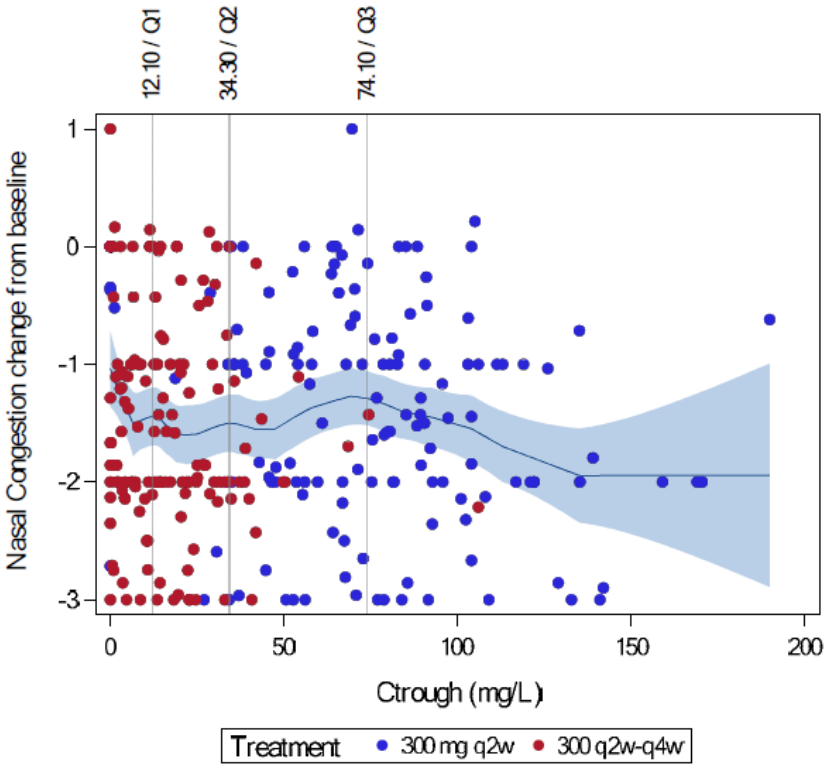
1 Least square means (95% CI) from ANCOVA model

2 Predicted mean (95% CI) at median E_{max} and median C_{trough}

Quartile Plot and Summary Table at Week 52

The NC response over the exposure quartiles appeared to be generally similar.

Scatter Plot of NC Change from Baseline against Ctrough (mg/L) at Week 52 (Study EFC14280)



Summary of NC Change from Baseline by Ctrough (mg/L) Quartile at Week 52 (Study EFC14280)

Quartile	Number of patients	NC Change Mean	NC Change Range	NC Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error	Number of patients: 300 mg q2w:300 mg q2w-q4w
1	72	-1.303	(-3.000,1.000)	0.119	3.98	(0.04,12.10)	0.46	9:63
2	72	-1.518	(-3.000,0.125)	0.113	22.67	(12.30,34.30)	0.83	8:64
3	72	-1.370	(-3.000,1.000)	0.115	53.68	(34.78,74.10)	1.45	58:14
4	71	-1.585	(-3.000,0.214)	0.101	102.4	(74.40,189.9)	2.97	69:2

Quartile values: Q1= 12.1; Q2= 34.3; Q3= 74.1 mg/L

To evaluate the impact of treatment discontinuation, sensitivity analyses were conducted by excluding subjects who discontinued the treatment.

Exposure-Response Model at Week 52

An Emax model was selected as the best base model. The EC50 was stably estimated but with a large confidence interval, which reflected the data variability. Higher baseline TARC or higher baseline NC score were associated with significantly increased placebo-adjusted treatment effect at Week 52.

Nasal Congestion Score Change from Baseline vs. Ctrough at Week 52: the PK/PD Model Parameter Estimations (Study EFC14280)

Parameter	Estimate	95% CI	Standard Error	P-value
b0	-0.418	-0.627 , -0.209	0.106	<.0001
b1: baseline Nasal Congestion - median NC	-0.327	-0.573 , -0.081	0.125	0.0092
b2: Asia vs Western	-0.004	-0.254 , 0.245	0.127	0.9733
b3: Latin America vs Western	0.156	-0.031 , 0.343	0.095	0.1021
b4: East Europe vs Western	0.023	-0.24 , 0.286	0.134	0.8646
b5: asthma/NERD status=Y	-0.082	-0.243 , 0.078	0.082	0.3130
b6: Prior NP surgery=Y	0.062	-0.106 , 0.231	0.086	0.4686
b7: Baseline ln(TARC)-median baseline ln(TARC)	0.232	0.012 , 0.453	0.112	0.0392
Emax0	-1.154	-1.318 , -0.991	0.083	<.0001
Emax1: Baseline nasal congestion - median NC	-0.418	-0.713 , -0.124	0.150	0.0055
Emax2: Baseline ln(TARC) - median baseline ln(TARC)	-0.399	-0.668 , -0.13	0.137	0.0038
EC_{50} (mg/L)#	0.078	-0.019 , 0.176	0.050	0.1145
sigma**2	0.611	0.529 , 0.693	0.042	<.0001

#EC_{50} with unit mg/L was estimated with wide 95% CI covering 0.

LOSS OF SENSE OF SMELL (LOSS)

For the secondary endpoints, LOSS and SNOT-22, a generally flat E-R relationship was observed for both endpoints at Week 24 and Week 52

Quartile Plot and Summary Table at Week 24

Figure 13 - Scatter Plot of Loss of Sense of Smell Change from Baseline against Observed C_{trough} (mg/L) at Week 24 (Studies EFC14146 and EFC14280)

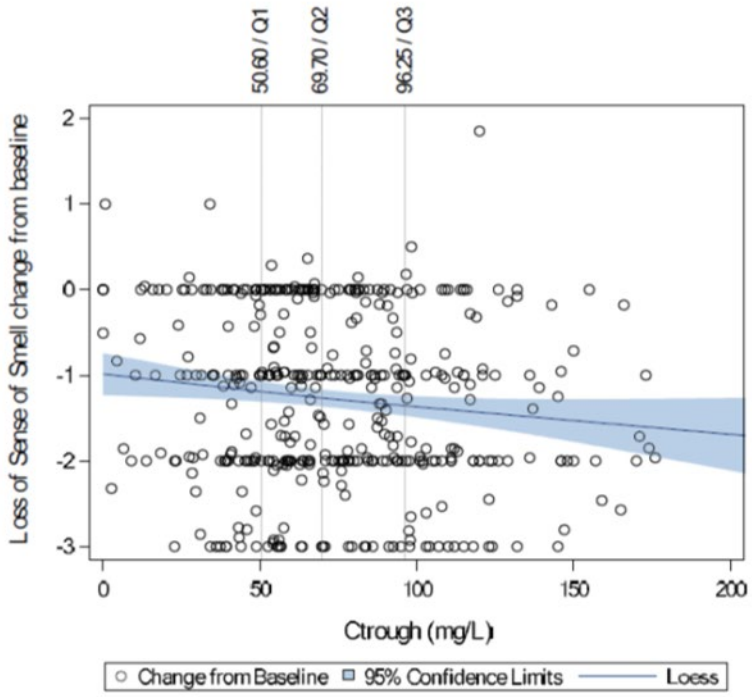


Table 19 - Summary of Loss of Sense of Smell Change from Baseline by Observed C_{trough} (mg/L) Quartile at Week 24 (Studies EFC14146 and EFC14280)

Quartile	Number of patients	LOSS Change Mean	LOSS Change Range	LOSS Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error
1	105	-1.161	(-3.000,1.000)	0.103	33.77	(0.04,50.50)	1.37
2	106	-1.157	(-3.000,0.363)	0.097	59.99	(50.70,69.70)	0.53
3	104	-1.316	(-3.000,0.143)	0.091	83.31	(70.10,96.10)	0.73
4	105	-1.485	(-3.000,1.852)	0.101	122.6	(96.40,208.0)	2.33

Quartile values: Q1= 50.6; Q2= 69.7; Q3= 96.25 mg/L

Quartile Plot and Summary Table at Week 52

A relatively flat curve of LOSS change score from baseline as the Ctrough increases was observed up to 100 mg/L.

Figure 14 - Scatter Plot of LOSS Change from Baseline against C_{trough} (mg/L) at Week 52 (Study EFC14280)

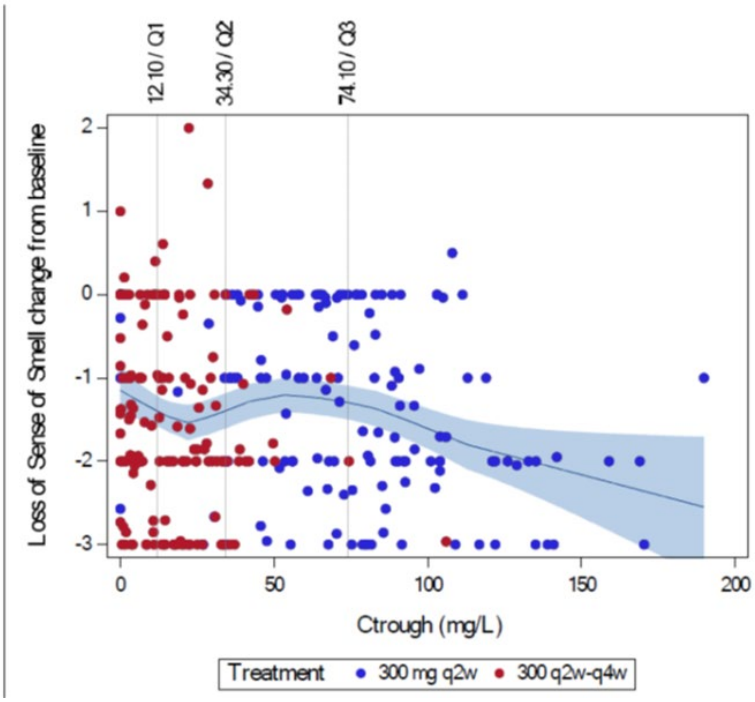


Table 20 - Summary of Loss of Sense of Smell Change from Baseline by C_{trough} (mg/L) Quartile at Week 52 (Study EFC14280)

Quartile	Number of patients	LOSS Change Mean	LOSS Change Range	LOSS Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error	Number of patients: 300 mg q2w:300 mg q2w-q4w
1	72	-1.248	(-3.000,1.000)	0.130	3.98	(0.04,12.10)	0.46	9:63
2	72	-1.572	(-3.000,2.000)	0.140	22.67	(12.30,34.30)	0.83	8:64
3	72	-1.088	(-3.000,0.000)	0.120	53.68	(34.78,74.10)	1.45	58:14
4	71	-1.667	(-3.000,0.500)	0.123	102.4	(74.40,189.9)	2.97	69:2

Quartile values: Q1= 12.1; Q2= 34.3; Q3= 74.1 mg/L

TWENTY TWO ITEM SINO-NASAL OUTCOME TEST (SNOT-22)

Quartile Plot and Summary Table at Week 24

Figure 16 - Scatter Plot of SNOT-22 Change from Baseline against Observed C_{trough} (mg/L) at Week 24 (Studies EFC14146 and EFC14280)

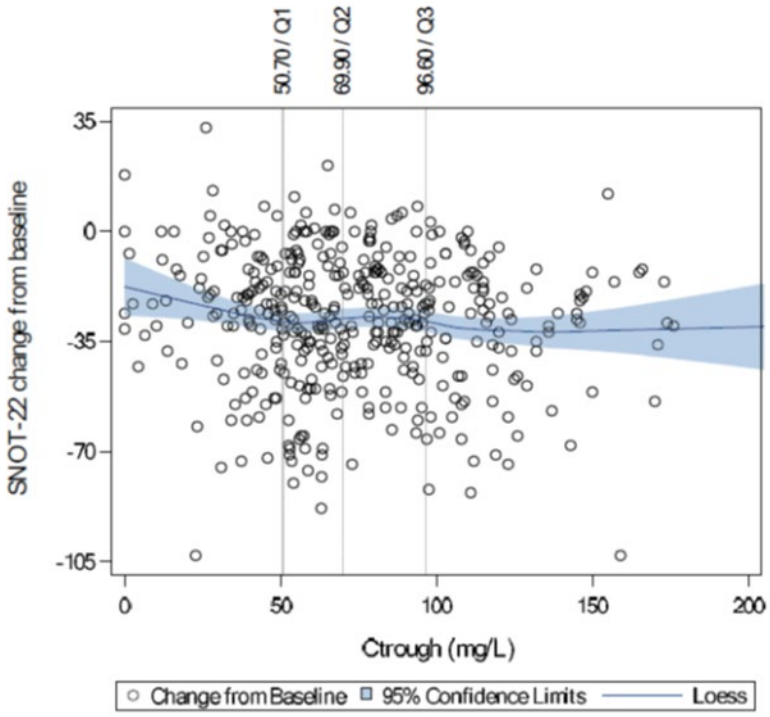


Table 22 - Summary of SNOT-22 Change from Baseline by Observed C_{trough} (mg/L) Quartile at Week 24 (Studies EFC14146 and EFC14280)

Quartile	Number of patients	SNOT-22 Change Mean	SNOT-22 Change Range	SNOT-22 Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error
1	102	-25.15	(-103.0,33.000)	2.126	33.67	(0.04,50.50)	1.39
2	102	-30.03	(-88.00,21.000)	2.374	60.03	(50.90,69.70)	0.54
3	103	-26.46	(-74.00,8.000)	1.732	83.84	(70.10,96.60)	0.75
4	101	-31.29	(-103.0,12.000)	2.175	123.4	(96.90,208.0)	2.38

Quartile values: Q1= 50.7; Q2= 69.9; Q3= 96.6 mg/L

Quartile Plot and Summary Table at Week 52

A relatively flat curve of SNOT-22 change score as the Ctrough increases was observed.

Figure 17 - Scatter Plot of SNOT-22 Change from Baseline against C_{trough} (mg/L) at Week 52 (Study EFC14280)

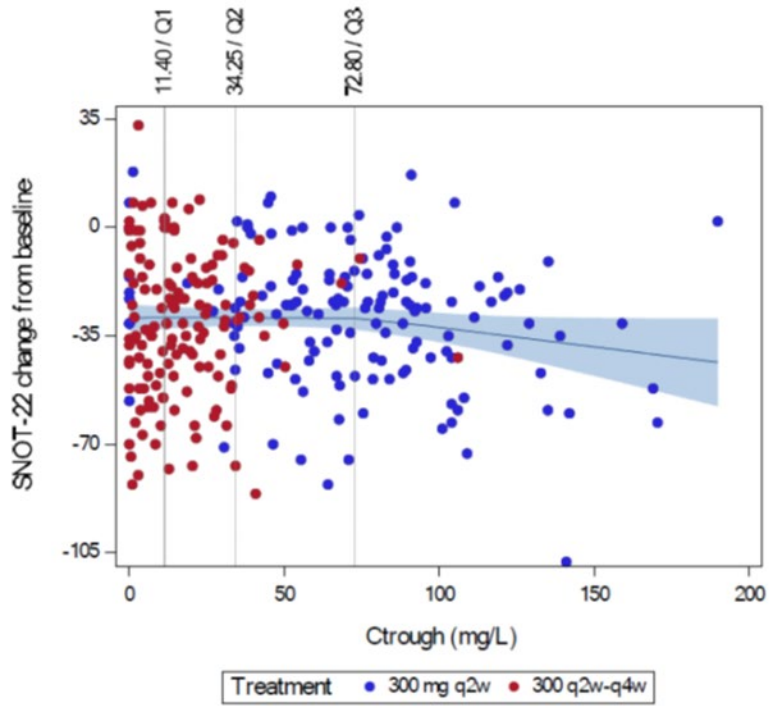


Table 23 - Summary of SNOT-22 Change from Baseline by C_{trough} (mg/L) Quartile at Week 52 (Study EFC14280)

Quartile	Number of patients	SNOT-22 Change Mean	SNOT-22 Change Range	SNOT-22 Change Standard Error	C_{trough} Mean	C_{trough} Range	C_{trough} Standard Error	Number of patients: 300 mg q2w:300 mg q2w-q4w
1	71	-29.41	(-83.00,33.00)	3.110	3.86	(0.04,11.40)	0.45	10:61
2	70	-30.69	(-78.00,9.00)	2.425	22.24	(12.10,34.20)	0.83	8:62
3	71	-27.87	(-86.00,10.00)	2.590	52.98	(34.30,72.80)	1.46	56:15
4	70	-31.06	(-108.0,17.00)	2.552	102.3	(74.10,189.9)	3.02	68:2

Quartile values: Q1= 11.4; Q2= 34.25; Q3= 72.8 mg/L

Sensitivity analyses

In the sensitivity analyses, the results of the completers were consistent with those where subjects who discontinued treatment were excluded for all four efficacy endpoints.

2.3.5. Discussion on clinical pharmacology

Analytical methods

For functional dupilumab, study / disease specific incurred reanalysis data shows that the concentration obtained for the initial analysis and the concentration obtained by reanalysis was within 30% of their mean for at least 87.5% of the repeats. This is acceptable to use a method that has been validated for other disease types and in-line with EU guidance.

The PK and PD profiles of dupilumab were assessed in adult patients with CRSwNP who were inadequately controlled with INCS and had failed prior treatment with systemic corticosteroids and/or surgery. In the Phase 2a study ACT12340 and 2 pivotal Phase 3 studies (EFC14146 and EFC14280) for treatment periods ranged from 16 weeks to 52 weeks. A subcutaneous (SC) dosing regimen of 300 mg once every week (qw), following a loading dose of 600 mg on Day 1, was assessed in this Phase 2a study. Subsequently, the 300 mg once every 2 weeks (q2w) regimen without a loading dose was evaluated in Studies EFC14146 and EFC14280, and the 300 mg once every 4 weeks (q4w) regimen was evaluated following 24 weeks of 300 mg q2w treatment in Study EFC14280.

Pharmacokinetics

In patients with CRSwNP, dupilumab is well-absorbed with an estimated subcutaneous (SC) bioavailability of 62.8%, distributes primarily within the vascular compartment (4.91 L) and exhibits non-linear target-mediated elimination. Based on Pop PK analysis, the median time to steady state was 16 weeks for 300 mg q2w. At steady state, the mean trough concentration was 74.4 to 80.2 mg/L. In study EFC14280 following the switch to the 300 q4w dosing regimen at week 24, a new steady state was achieved after additional 24 weeks. The mean trough concentration decreased from 75.5 mg/L at Week 24 to 17.6 mg/L at Week 52. The data show that the pharmacokinetic of dupilumab is similar in healthy subjects, CRSwNP, asthma, and AD patient populations.

The proposed dose regimen by the applicant is 300 mg q2w for dupilumab. In the pivotal phase 3 studies this dosing regimen demonstrated statistically significant and clinically meaningful improvements with regards to the co-primary and the secondary efficacy endpoints. It was also demonstrated that continued dosing is necessary for maintenance of efficacy. In Study EFC14146 in which benefits were lost when patients were removed from treatment compared to patients in study EFC14280 who continued on this regimen beyond Week 24 and showed sustained efficacy in most efficacy endpoints. The benefits were numerically greater for patients maintained on the 300 mg q2w regimen beyond Week 24 compared to patients who switched to a 300 mg q4w regimen at Week 24 (Study EFC14280). A descriptive exposure-efficacy analysis by quartile of dupilumab concentrations was conducted to examine the apparent correlation of the response with the trough concentrations. Over the narrow exposure range of 300 mg q2w at Week 24, there was no concentration-related increase in NPS and NC response. Over a wider exposure range of 300 mg q2w and 300 mg q2w-q4w regimens pooled together, NPS improvement at Week 52 for the lowest exposure quartile (Q1) was numerically smaller than the other 3 quartiles of exposure. This suggests a greater efficacy for the 300 mg q2w regimen compared to the 300 mg q2w-q4w regimen since the majority of patients in Q1 (96%) received 300 mg q2w-q4w.

In addition, TEAEs of sinusitis, headache, nasal polyps, and asthma were reported more frequently by patients after switching to the 300 mg q4w regimen at Week 24. The safety data support the efficacy and PK data indicating that the 300 mg q2w-q4w regimen may provide suboptimal disease control with regards to long term treatment compared to the 300 mg q2w regimen.

Based on the CRSwNP Pop PK model-based post hoc estimates, cross study comparison of $AUC_{T,ss}$ at steady state, mean $AUC_{T,ss}$ were similar for 300 mg q2w to 300 mg qw, indicating no major deviation from dose proportionality between 300 mg q2w to 300 mg qw and suggesting a saturation of the target-mediated elimination at doses of 300 mg q2w and higher.

For the 300 mg q2w−q4w group, the PK profile was similar to 300 q2w group from baseline to Week 24. After the switch from the 300 mg q2w to 300 mg q4w dosing regimen at Week 24, mean trough concentration decreased from 75.5 mg/L at Week 24 to 17.6 mg/L at Week 52. The mean trough concentration increased in a greater than dose-proportional manner at Week 52 (4.29-fold [17.6 versus 75.5 mg/L] for a 2-fold dose increase from 300 mg q4w to 300 mg q2w). Some

patients may not have reached full saturation of the target-mediated elimination at the steady-state exposure of 300 mg q4w. Of note, more patients in the 300 mg q2w-q4w regimen had steady-state concentrations at the end of the 52-week treatment that were below the limit of quantitation (0.078 mg/L) compared to the300 mg q2w regimen.

Population PK Analyses

The effect of intrinsic and extrinsic factors on dupilumab PK in patients with CRSwNP was evaluated via Pop PK analysis. The CRSwNP Pop PK strategy involved the development of a global Pop PK base model first, with pooled data from healthy subjects and patients with AD and asthma patients (Study POH0668). This base model was then extended to allow the identification of covariates in a Pop PK model for the CRSwNP population using pooled data from Phase 2 and pivotal Phase 3 studies in adult patients with CRSwNP (Study POH0611).

Study POH0668

The population PK analysis was conducted acceptably. A global Pop PK base model was developed, which adequately described the PK of functional dupilumab in AD and asthma patients by a 2-compartment model with parallel linear and nonlinear elimination with first order absorption.

Consistent with previous AD and asthma Pop PK models, and due to its notable effect on dupilumab PK, body weight was included in the base model to explain between-subject variability of steady state exposure of dupilumab in AD and asthma patients, which is acceptable.

The model-simulated PK profiles were in good agreement with the observed PK profiles in AD and asthma populations, which support the predictability of this global Pop PK base model across a wide dose range for other type 2 inflammatory disease populations such as CRSwNP.

Study POH0611

Overall, the popPK analysis was conducted acceptably. The final two-compartment model with parallel linear and nonlinear elimination with first order absorption adequately described the PK of dupilumab in adult patients with nasal polyposis (NP). PK parameters were estimated with acceptable precision. No systematic deviations or major bias in any of the goodness of fit plots were observed and the predictive performance of the model was acceptable based on bootstrap and VPCs.

Body weight was found to be the primary source of dupilumab PK variability in the NP population. All other covariates, including age, gender, race, baseline lab parameters (creatinine clearance and albumin), baseline biomarker (EoS), disease severity (NPS, NC, UPSIT), and ADA, were not found to have a statistically significant effect on dupilumab PK in NP patients. Additionally, concomitant medications (intranasal corticosteroid spray once or twice a day, oral corticosteroids, systemic antihistamines, and allergen immunotherapy) and comorbidity with asthma were not found to have a significant effect on dupilumab PK based on post-hoc predicted exposures. The applicant claims that the apparent difference in PK exposures across age, race and CLCR groups is mainly explained by the difference in body weight, which is considered plausible. However, the impact of severely impaired renal and hepatic function on dupilumab PK is not known and the existing statements relating to this in Sections 4.2/5.2 of the SmPC are considered acceptable. The assessment of the impact of ADA was based on limited data, with most of the ADA positive responses being of low titer and very few of moderate or high titers. Consequently, the exposures in the few high titer patients were over-estimated by final NP Pop PK model (see below for further discussion on immunogenicity).

The impact of body weight on dupilumab steady state exposure variables was assessed using simulations. At the proposed dose of 300 mg q2w, exposures were ~60% higher and ~35% lower in patients weighing 53 kg and 110 kg, respectively, compared to a typical 79 kg patient. However, the highest and lowest weights in the data set were 150 kg and 38 kg, respectively, and, therefore, even greater differences in exposure are likely to be observed in patients at these extremes of weight. Further clarification it was considered that the observed changes were not clinically relevant for adjustment of dosing regimen.

Pharmacodynamics

Across the Phase 2 and Phase 3 program in CRSwNP, blood levels of the type 2 inflammation biomarkers (thymus and activation-regulated chemokine [TARC], total IgE, eosinophil cationic protein [ECP], and periostin) were assessed as markers for disease activity/severity and to gain a better mechanistic understanding of dupilumab action. These same markers and eotaxin-3 were also assessed from nasal secretions to similarly gain an understanding of dupilumab's actions in the sino-nasal cavity. In addition, the dupilumab effect on leukotriene E4 (LTE4) in urine, a stable end product of the cysteinyl leukotriene pathway and a marker of activation of mast cells, involved in type 2 inflammation in patients with CRSwNP and NSAID-ERD, was explored.

The concentration of these biomarkers declined during treatment with dupilumab, which was expected based on mechanism of action of dupilumab. There was a substantial reduction of TARC concentration in serum with dupilumab treatment, with maximum effect achieved at the first post-baseline measurement and which was sustained over the treatment period for the 300 mg q2w and 300 mg q2w-q4w regimens. Dupilumab suppression of total IgE gradually developed over time, with greater effect observed with longer treatment. These results support the effective blockage of IL-4/IL-13 mediated type 2 signalling via IL-4Rα by dupilumab in type 2 driven diseases. Concomitantly, reductions of eotaxin-3, total IgE, and ECP concentrations in nasal secretions were observed with dupilumab treatment, indicating a direct effect on type 2 biomarkers in the target sino-nasal tissue for CRSwNP. Urinary LTE4, a marker of mast cell activation involved in type 2 inflammation, was suppressed by dupilumab treatment. In patients with NSAID-ERD, where LTE4 is particularly elevated, there was a marked decrease in urinary level as well. The reduction in biomarkers was already seen at the first assessment at Week 24 and was sustained through Week 52 in patients on both dupilumab dosing regimens.

Pharmacokinetic/Pharmacodynamic Relationships

The objectives of the empirical PK/PD analyses in this study were to understand dupilumab E-R relationships in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) with regard to the key efficacy endpoints, and to identify covariates influencing E-R relationships. The analysis was intended to support the proposed labeling dose regimen for dupilumab as add-on treatment in adult patients with severe CRSwNP who are inadequately controlled with intranasal corticosteroids. Descriptive as well as model-based E-R analyses were conducted using the trough concentration (Ctrough) of dupilumab for analyses of four efficacy endpoints, nasal polyps score (NPS), nasal congestion (NC), loss of sense of smell (LOSS) and 22-item sino-nasal outcome test (SNOT-22), at Week 24 (pooled for the 2 pivotal studies, EFC14146 and EFC14280) and at Week 52 (Study EFC14280 only).

Descriptive quartile analysis showed no exposure- related increase in NPS and NC response over the exposure range of 300 mg q2w at Week 24. Over a wider exposure range of 300 mg q2w and 300 mg q2w-q4w regimens pooled together, improvement in NPS at Week 52 for the lowest exposure quartile was numerically smaller than the other three higher quartiles of exposure. However, similar analyses of other endpoints, NC, SNOT-22, LOSS did not show a clinically meaningful increase from the lowest exposure quartile to the other three higher quartiles of exposure at Week 52.

Model-based analyses showed a sigmoidal Emax relationship between primary efficacy endpoint (NPS and NC, absolute change from baseline) and dupilumab Ctrough. E-R modeling of NPS indicated that the treatment effect approached, but did not reach Emax, at the exposure of 300 mg q2w-q4w and reached a plateau at the exposure of 300 mg q2w, supported by a numerically greater improvement in NPS for 300 mg q2w compared to 300 mg q2w-q4w at Week 52. For NC, the E-R relationship appeared flat over the concentration range studied.

Overall, the PK/PD analyses of key efficacy endpoints did not show a concentration-related increase in efficacy over a narrow range for 300 mg q2w, but did show a slight improvement in NPS response over a wider range of exposure combined for 300 mg q2w and 300 mg q2w-q4w.

Immunogenicity

The ADA response in CRSwNP patients was consistent with that observed for asthma and AD patients at the same dupilumab dose and treatment duration.

Due to the different measurement time points and limited patient numbers in Study ACT12340, the pool of dupilumab 300 mg q2w arms in Studies EFC14146 and EFC14280 was the principal source of data to evaluate ADA responses in patients with CRSwNP with the same treatment duration (24 weeks). The incidence of treatment-emergent ADA was 4.3% in the 300 mg q2w group compared to 2.1% in the placebo group. Persistent ADA response was seen in 1.6% of all patients at 300 mg q2w compared to 0.7% for placebo. Most of the treatment emergent ADA responses were low titer. High titer ADA response (>10 000) was observed in 0.9% of patients treated with dupilumab and was not observed in patients on placebo. Approximately 2.5% of all patients at 300 mg q2w were classified as neutralizing antibody (NAb) positive compared to 0.7% in the placebo group. The treatment-emergent ADA incidence was similar (2.1 to 4.8%) following dupilumab treatment for 24 weeks (300 mg q2w in Study EFC14146) or 52 weeks (300 mg q2w and 300 mg q2−q4w in Study EFC14280) as well as placebo treatment (0.7% to 4.8% in Studies EFC14146 and EFC14280). The ADA incidence was similar across the CRSwNP, AD, and asthma populations with respect to treatment emergent positive ADA response (5-6%), persistent ADA response (~2%), and neutralizing antibody response (1-3%) after 52 weeks of treatment at 300 mg q2w.

The antibody titers detected in both dupilumab and placebo patients with CRSwNP were mostly low and did not correlate with clinically meaningful differences in dupilumab efficacy or safety, except for the rare cases where patients developed high-titer antibodies to dupilumab. In these patients lower dupilumab concentrations were observed and an effect on the results of the efficacy endpoints was seen.

2.3.6. Conclusions on clinical pharmacology

Results of the PK/PD analyses are consistent with the efficacy evaluation in patients with CSRwNP. The totality of these data supports dupilumab 300 mg q2w as the more effective dose for long term treatment as an add-on treatment in adult patients with severe CRSwNP who are inadequately controlled with INCS. However, continued improvements through 52 weeks of treatment with both dosing regimens suggest that the maximal treatment effect had not been reached by the end of study EFC 14280.

A descriptive exposure-efficacy analysis by quartile of dupilumab concentrations was conducted to examine the apparent correlation of the response with the trough concentrations. Over the narrow exposure range of 300 mg q2w at Week 24, there was no concentration-related increase in NPS and NC response. Over a wider exposure range of 300 mg q2w and 300 mg q2w-q4w regimens pooled together, NPS improvement at Week 52 for the lowest exposure quartile (Q1) was numerically smaller than the other 3 quartiles of exposure. This further supports the 300 mg q2w regimen compared to the 300 mg q2w-q4w regimen since the majority of patients in Q1 (96%) received 300 mg q2w-q4w.

Therefore, the recommended dose of dupilumab for adult patients with CRSwNP is an initial dose of 300 mg followed by 300 mg given every other week.

The ADA response in CRSwNP patients is consistent with that observed for asthma and AD patients at the same dupilumab dose and treatment duration.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose response study was performed in patients with nasal polyps.

The dose regimens were selected based on the totality of clinical evidence in the dupilumab program including data from Phase 2 efficacy and safety study (ACT12340) in patients with nasal polyps and symptoms of chronic sinusitis, the result of Phase 2b dose ranging study in patients with moderate to severe asthma (DRI12544), the Phase 2b dose ranging study (R668-AD-1021) and phase 3 studies (R668-AD-1334 and R668-AD-1416) in patients with moderate to severe atopic dermatitis (AD), as well as the supportive PK/pharmacodynamic [PD] analysis.

In study ACT12340, 600 mg loading dose was followed by 300 mg given every week. The proposed dosing regimen and doses tested in pivotal studies deviates from the one that was tested in study ACT12340 (i.e. q2w instead of weekly dosing; no loading dose).

The SNOT-22 results from 300mg q2w being used in asthma patients with NP as co-morbidity were discussed and used as a justification for the selected dose. In asthma dose ranging study (DRI12544), 300 mg q2w regimen demonstrated a robust treatment effect across all relevant indices of drug action, while a lower dose or a less frequent regimen 200 mg q2w and 300mg q4w showed less effect in some endpoints including SNOT-22.

The simulated concentration-time profiles for dupilumab in typical CRSwNP patients receiving 300 mg q2w with or without a loading dose of 600 mg (-please see discussion in the PK section) confirmed that the absence of loading dose results in longer time to steady state, but does not impact the steady state level. In addition, PK/PD simulation of co-primary endpoints of NPS and NC showed minimal difference in the development of treatment effect and steady-state response of NPS and NC in the presence and absence of a loading dose of 600 mg on Day 1. It is agreed that the lack of a loading dose is justified.

2.4.2. Main studies

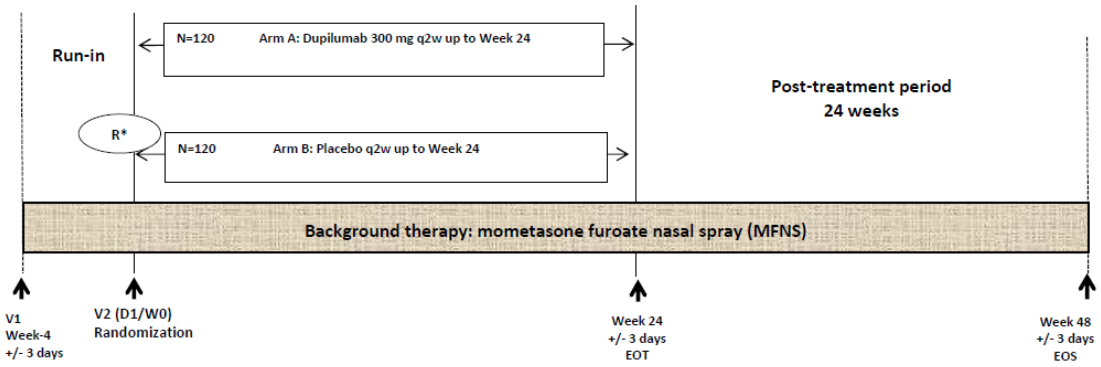
There were two pivotal studies (EFC14280 and EFC 14146) submitted in this application and a supportive study (ACT12340).

2.4.2.1. Study EFC14146

Title
EFC14146: a pivotal Phase 3 study evaluating the effect of dupilumab 300 mg administered subcutaneously every 2 weeks (q2w) for 24 weeks in patients with CRSwNP on a background therapy of MFNS.

Methods

Study design
Study EFC14146 was a randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids.



BID twice daily; D day; EOS end of study; EOT end of treatment; IMP investigational medicinal product; q2w every 2 weeks; MFNS mometasone furoate nasal spray; R* randomization; QD once daily; SC subcutaneous; V visit; W week

IMP: Regardless of the treatment group, all randomized patients received q2w SC administrations of dupilumab or placebo. Every other week IMP administrations were to be separated by at least 11 days. At V2 the Investigator or delegate performed the injection. After V2, every other week administration of IMP was to be performed at the investigational site up to at least Week 8 (Visit 6). Patients were monitored at the study site for at least 30 minutes or the minimum time required by local regulator after injections. From Week 10, every other week home administration of IMP (patient, caregiver, or health care professional) was possible if the patient (or the caregiver) had been trained. If the patient (or caregiver) was unable or unwilling to administer IMP, arrangements were to be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

Non-investigational medicinal product: MFNS was to be self-administered by the patient BID or QD (if they could not tolerate BID). At each visit the Investigator was to ensure that the patient had the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

The study consisted of 3 periods: a run-in period, a treatment period and a post treatment period.

In the run-in period (4 weeks) patient's eligibility was determined and the background intranasal corticosteroids were standardized prior to randomization. Patients were to receive MFNS, 2 actuations (50 µg/actuation) in each nostril twice daily (BID; total daily dose of 400 µg starting at V1). In the randomized treatment period (24 weeks) patients were randomized in a 1:1 ratio to dupilumab SC q2w or placebo matching dupilumab SC q2w. Randomization was stratified by the presence of comorbid asthma and/or NSAID-ERD), prior NP surgery (yes or no), and country. Patients were to continue the stable dose of intranasal MFNS established during the run-in period except if the dose was changed due to an adverse event (AE). In the post treatment period (24 weeks) patients were followed for 24 weeks to evaluate potential disease recurrence.

Study participants

276 patients with CRSwNP were randomized in this study (143 patients in the dupilumab treatment group and 133 patients in the placebo group).

The target Phase 3 study populations consisted of patients 18 years and older with high CRSwNP disease burden (based on polyps score) and symptoms of NC and loss of smell or rhinorrhea for at least 12 weeks prior to randomization (8 weeks prior to screening) despite therapy with intranasal corticosteroids, systemic corticosteroids in the past 2 years or sino-nasal surgery.

Randomization was stratified by asthma/NSAID-ERD status (yes/no), prior history of surgery for CRSwNP (yes/no), and country. Specific subgroup analyses were performed to assess efficacy in these subgroups in addition to the efficacy in the overall population.

Key inclusion and exclusion criteria for Study EFC14146

Inclusion Criteria	
Diagnostic criteria	Patients with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or who had a medical contraindication/intolerance to SCS; and/or had prior surgery for NP: • An endoscopic bilateral NPS at V1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) • Ongoing symptoms (for at least 8 weeks before V1) of: - Nasal congestion/ blockade/obstruction with moderate or severe symptom severity (score 2 or 3) at V1 and a weekly average severity of greater than 1 at time of randomization (V2) AND - Another symptom such as loss of smell, rhinorrhea (anterior/posterior).
Age	≥18 years
Exclusion Criteria	
Prior treatments	Patients who had taken • Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease within 2 months before Visit 1 or 5 half-lives, whichever is longer. • Any experimental monoclonal antibody (mAB) within 5 half-lives or within 6 months before Visit 1 • Anti-IgE therapy (omalizumab) within 130 days prior to Visit 1 • Patients receiving leukotriene antagonists/modifiers at Visit 1 unless on continuous treatment for at least 30 days prior to Visit 1 • Initiation of allergen immunotherapy within 3 months prior to Visit 1
FEV_1	Patients with forced expiratory volume in 1 second (FEV_1) 50% or less of predicted normal were excluded
Prior surgery	Patients who have undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months before screening and patients who had a sino—nasal surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS were excluded
Concomitant conditions/diseases	Antrochoanal polyps, nasal septal deviation that would occlude at least one nostril, acute sinusitis, nasal infection or upper respiratory tract infection, ongoing rhinitis medicamentosa, Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis, radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis

These inclusion criteria were consistent with the definition Rhinosinusitis as per European Position Paper on Rhinosinusitis and Nasal Polyps. In addition the Position Paper states: *Nasal polyps and chronic rhinosinusitis are often taken together as one disease entity, because it seems impossible to clearly differentiate between them.* Nasal Polyposis is therefore considered a subgroup of Chronic Rhinosinusitis.

Treatments

All randomized patients received Dupilumab 300 mg SC q2w (2 mL) or Placebo matched to dupilumab 300 mg (2 mL) q2w SC. Every other week IMP administrations were separated by at least 11 days.

Background treatment

Mometasone furoate (NASONEX®) 50 micrograms (µg)/actuation nasal spray was provided by the Sponsor in a bottle with 18 g (140 actuations) of product formulation. The patients were to administer 2 actuations (50 µg/actuation) of MFNS in each nostril twice daily (BID) (total daily dose of 400 µg) unless they were intolerant to the BID regimen or this dose was not approved in specific countries, in which case, they were to follow a once daily (QD) regimen.

Rescue treatment

- Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection).
- Short course SCS (prednisone or prednisolone up to 2 weeks).
- Sino-nasal surgery for nasal polyps. Based on previous observations from the POC study, 8 weeks of IMP treatment was recommended prior to surgery to allow onset of treatment effect.

Prohibited concomitant medications

The following concomitant treatments are not permitted during the run-in period and/or the

randomized treatment period:

- Any systemic immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrilomus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide.
- Anti-IgE therapy (omalizumab).
- Allergen immunotherapy (except if initiated more than 3 months prior to V1 and dose stable 1 month prior to V1).
- Intranasal corticosteroid drops.
- Long term courses (>2 weeks) of systemic steroids.
- Short term courses (≤2 weeks) of IV, IM, SC corticosteroids.
- Short course use (≤2 weeks) of OCS between V1 and V2.
- Live, attenuated vaccines (Appendix A).
- Monoclonal antibodies.

Permitted concomitant medications

- MFNS during the run-in period and throughout the whole study.
- Nasal normal saline.
- Single topical decongestants administration for example oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic for example lidocaine are allowed before endoscopy.
- Short term use of antibiotics (<2 weeks) are allowed during the study.
- Short-acting β2-adrenoceptor agonist, long-acting β2-adrenoceptor agonist and long-acting muscarinic antagonist.
- Methylxanthines (for example theophylline, aminophyllines).
- Inhaled corticosteroids.
- Systemic antihistamines.
- Leukotriene antagonists/modifiers are permitted during the study, only for patients who were on a continuous treatment for ≥30 days prior to V1.
- Allergen immunotherapy in place for ≥3 months prior to V1 is permitted.

Objectives

The primary objective of study 14146 was to evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of MFNS in reducing NC/obstruction severity and endoscopic nasal polyps score (NPS) in patients with bilateral NP.

The secondary objectives included evaluation of the efficacy of dupilumab in improving total symptoms score (TSS), the efficacy of dupilumab in improving sense of smell, the efficacy of dupilumab in reducing CT scan opacification of the sinuses, the ability of dupilumab to reduce the proportion of patients who require treatment with SCS or surgery for NP, the efficacy of dupilumab on patient reported outcomes (PROs) and healthrelated quality of life (HRQoL) and the effect of dupilumab in the subgroups of patients with prior surgery and comorbid asthma (including NSAID-ERD).

Outcomes/endpoints

There were two co-**primary endpoints**:

- Change from baseline in nasal polyps score at Week 24

  The NPS was assessed by at least 2 physicians based on centrally read video recordings of nasal endoscopy. The score (NPS) was the sum of the right and left nostril scores (range 0 to 8), as evaluated by means of nasal endoscopy. Nasal polyp score was graded based on polyp size in each nostril as described in the Table below. There is no established MCID for NPS. In a study using the same NPS as the current study, a short course of methylprednisolone resulted in a peak difference versus placebo of approximately -2.2 points

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

- CHANGE FROM BASELINE IN NASAL CONGESTION/OBSTRUCTION (NC)

  Nasal congestion/obstruction was scored by the patient as a reflective score, evaluating the symptom severity over the past 24 hours. The NC score was to be recorded by the patient every morning in an e-diary, starting at screening and throughout the study, using the scale presented below.

Scale	Symptoms
0	No symptoms
1	Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated)
2	Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
3	Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

Secondary endpoints

Key secondary endpoints (hierarchically ordered to account for multiplicity is shown in table 5):

- Change from baseline in LMK score at week 24
- Change from baseline in TSS at Week 24
- Change from baseline in smell test (UPSIT) at Week 24
- Change from baseline in loss of smell daily symptoms at Week 24
- Change from baseline in SNOT-22 at Week 24

- Proportion of patients during study treatment receiving OCS for NP and/or planned to undergo surgery for nasal polyps

Additional secondary endpoints:

- Change from baseline and time course profiles in NPS, NC, LMK, TSS, UPSIT, daily assessed loss of smell, and SNOT-22 at Week 48,
- Change from baseline at Week 24 in: VAS for overall rhinosinusitis, NPIF, VAS for EQ-5D, and in the severity of rhinorrhea (anterior/posterior nasal discharge) daily symptom score assessed by the patient,
- Percentage change from baseline at Week 24 and time course profiles in: NC, Daily assessed loss of smell, TSS
- Percentage change from baseline at Week 24 in VAS for overall rhinosinusitis
- Proportion of responders at Week 24 (defined as patients with improvement by at least 1 point in NPS),
- Proportion of responders at Week 24 (defined as patients with improvement by at least 2 points in NPS),
- Proportion of patients with improvement by at least 1 point in NPS and 0.5 reductions in NC at Week 24 and Week 48,
- Proportion of patients with greater than or equal to the minimal clinically important difference (MCID)(≥8.9) in SNOT-22 at Week 24,
- Proportion of patients with overall rhinosinusitis severity VAS ≤7 at Week 24,
- The cumulative distribution function (CDF) of change from baseline in NC, NPS, SNOT-22 and VAS for rhinosinusitis severity at Week 24,
- Proportion of patients with anosmia by UPSIT scores at Week 24.

Sample size

The sample size was chosen to enable an adequate characterization of the difference in efficacy between dupilumab 300 mg q2w and placebo with regard to the 2 co-primary endpoints, changes from baseline in NC and NPS at Week 24. With a sample size of 120 patients per group, the combined power of the 2 co-primary efficacy endpoints was at least 93% for dupilumab 300 mg q2w group with alpha = 0.05 assuming no negative correlation between the 2 endpoints.

The observed mean NC reduction of the dupilumab group with qw dosing in ACT12340 is 0.95 and the observed mean NC reduction of the placebo group is 0.26. To calculate the power, a conservative estimate is used that assumes the placebo adjusted NC reduction of the dupilumab 300 mg q2w group is 80% of the effect observed with dupilumab 300 mg qw. Thus, the mean NC reduction of the dupilumab 300 mg q2w is then assumed to be 0.81 = 0.8 * (0.95 – 0.26) + 0.26 at Week 24. Assuming normal distribution of the change in NC, a common standard deviation (SD) of 1.03, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 95% power to detect an effect size of 0.534 using a two-sided test with alpha = 0.05 for the change in NC at Week 24 in the dupilumab 300 mg q2w group versus placebo.

The observed mean NPS reduction of the dupilumab group with qw dosing in ACT12340 is 1.85 and the observed mean NPS reduction of the placebo group is 0.30. Using the same conservative approach that assumes the placebo adjusted NPS reduction with the dupilumab 300 mg q2w is 80% of the effect observed with dupilumab 300 mg qw, the mean NPS reduction of the dupilumab 300 mg q2w group is then assumed to be 1.54 = 0.8 * (1.85 – 0.30) + 0.30. Assuming normal distribution of the change in NPS, a common SD of 2.11, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 120 patients per group, the study will have 98% power to detect an effect size of 0.588 using a two-sided test with alpha=0.05 for the change in NPS at Week 24 in the dupilumab 300 mg q2w group versus placebo.

Randomisation
Patients who meet the entry criteria were be randomized to one of the following treatment arms using a 1:1 randomization ratio:

• Arm A: dupilumab 300 mg SC q2w until Week 24.

• Arm B: placebo matching dupilumab SC q2w until Week 24.

A total of 240 (120 patients/arm) patients was planned to be randomized. Randomization was to be stratified based on asthma status (history of asthma or not), prior surgery (yes or no) and country. In order to have adequate number of patients for the subgroup analysis of patients with asthma/NERD and prior surgery enrolment of the following categories of patients were limited as follows (see rationale Section 4.2):

• Patients without asthma and/or NERD history will be limited to 120 patients (out of the total 240 randomized patients).

• Patients without prior surgery will be limited to 120 patients (out of the total 240 randomized patients).

Blinding (masking)
Dupilumab and placebo will be provided in identically matching 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab/placebo) glass prefilled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labelled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi. Both the patient and Investigator will be blinded to assigned active drug or placebo for the whole study period. Study patients, Investigators, and study site personnel will not have access to the randomization code list except under circumstances.

Statistical methods
The baseline value of efficacy parameters was defined as the last available value up to randomization but prior to the first dose of IMP, unless otherwise specified.

The primary analysis population for the efficacy endpoints included the randomized ITT population which includes all patients who were allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses were conducted according to the treatment to which they were randomized.

<u>Primary statistical model (ITT analysis)</u>

Each of the co-primary efficacy endpoints was analysed using a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation (MI). Data collected after treatment discontinuation were included in the analysis. The imputed completed data were analysed by fitting an analysis of covariance (ANCOVA) model with the baseline value of the corresponding co-primary endpoint, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

<u>Supportive and sensitivity analysis</u>

For all sensitivity analyses, except for the as-observed analysis, for patients who underwent surgery for NP or received SCS for any reason, data collected post-surgery or post SCS were be set to missing. The sensitivity analyses are summarized below.

- Mixed-effect model with repeated measures (MMRM) approach: The model included change from baseline values up to week 24 as response variables, and factors (fixed effects) for

treatment, stratification factor (comorbid asthma/NSAID-ERD, prior surgery, region), visit, treatment-by-visit interaction, NPS/NC baseline value and baseline-by-visit interaction. No imputation was performed for the MMRM model.

- Pattern mixture model with copy increment from placebo: Each of the 2 co-primary efficacy endpoints (3 co-primary efficacy endpoints for Japan) were analysed with imputed missing value at 24 weeks using pattern mixture model with copy increment from placebo (34). This copy increment from placebo implies that when subjects discontinue treatment early, they continue to take advantage of their previous therapy, but they progress in the same way as subjects in the placebo group. The imputed dataset was analysed by fitting an ANCOVA model same as the one in primary analysis.
- Tipping point analysis: Each of the 2 co-primary efficacy endpoints (3 co-primary efficacy endpoints for Japan) were analysed with imputed missing value at 24 weeks.
- As-observed analysis: An additional analysis was conducted on the co-primary efficacy endpoints which included all data (including that collected after SCS for any reason and/or treatment discontinuation) but excluded post NP surgery data. The data were analysed in the same ANCOVA model for the primary approach.
- Mixed-effect model with repeated measures (MMRM) approach for NC as binary response data: In the primary analysis, NC was analysed as the average of 28-day NC data. To assess the robustness of this approach, an MMRM approach on NC as longitudinal binary response data was performed based on methods proposed and evaluated by Fan.
- Subgroup analyses: To assess the consistency in treatment effects across different subgroup levels, subgroup analyses were conducted for the co-primary efficacy endpoints with respect to age, gender, region, territory, race, ethnicity, baseline weight, baseline BMI, prior NP surgery, asthma comorbidity and/or NSAID-ERD, and SCS use in the prior 2 years.

Analysis of key secondary endpoints

The change from baseline in sinus opacification CT scan score (LMK), TSS, UPSIT score, daily loss of smell, and SNOT-22 at Week 24 were assessed for dupilumab 300 mg q2w (Arm A) versus placebo (Arm B) and were analysed using the hybrid method of the WOCF and the MI in the same way as the primary approach of the co-primary endpoints. (Note: LMK was a co-primary and not a secondary endpoint for Japan).

Proportion of patients requiring rescue treatment (defined as use of SCS or NP surgery during the treatment period) was derived and analysed using the Cox proportional hazards model. The decision date of NP surgery or the first SCS intake date was used as the event date, or whichever was earlier if both occurred.

Due to the potentially low predicted number of patients requiring rescue treatment, the primary analysis for this endpoint was conducted by pooling the 2 Phase 3 CRSwNP studies, ie, the current study and Study EFC14280.

The change from baseline in FEV1 at Week 24 was assessed in patients with asthma. The analysis was conducted by pooling the 2 CRSwNP studies (the current study and Study EFC14280). The missing data in FEV1 at Week 24 was imputed using the hybrid method of the WOCF and the MI in the same way as the primary approach of the co-primary endpoints. The results of the pooled analysis are provided in Module 2.7.3 Summary of Clinical Efficacy, and the results of the analyses from the individual studies are provided in the respective CSRs.

Multiplicity issues

A hierarchical testing procedure was prespecified to control the overall type-I error rate for testing the co-primary and selected secondary endpoints. The overall alpha was 0.05. The comparisons with placebo were tested based on the hierarchical order in Table 5 at 2-sided α = 0.05.

Table 5 - Hierarchical testing order for coprimary and selected secondary endpoints

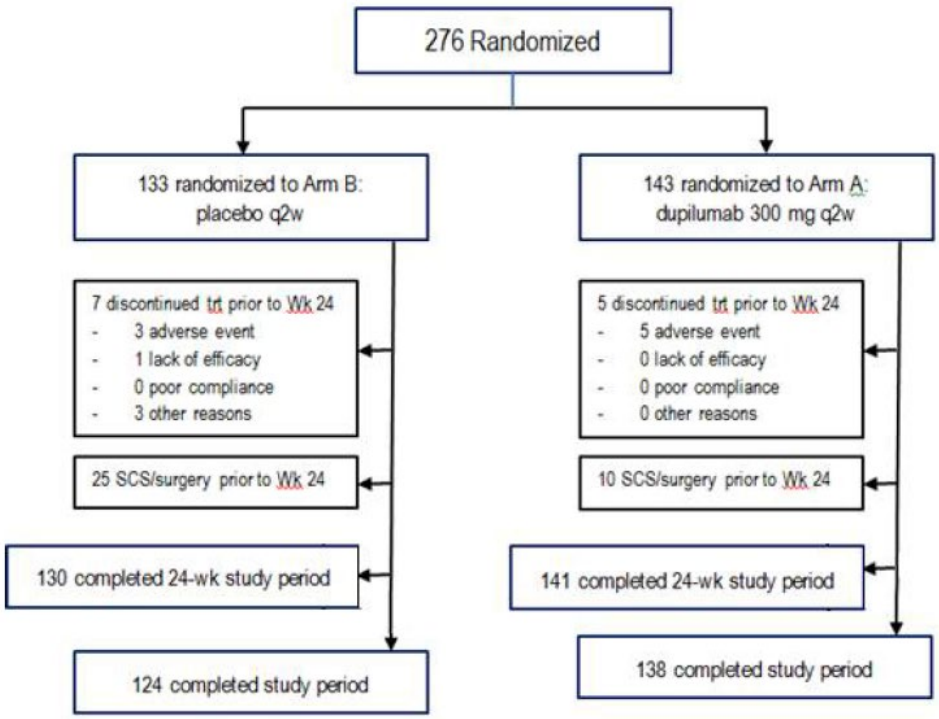
	Endpoints	Comparison
Coprimary	Change from baseline in bilateral NPS at Week 24	Dupilumab 300 mg q2w vs placebo
	Change from baseline in NC at Week 24	
Key secondary[a]	Change from baseline in LMK score at Week 24[b]	Dupilumab 300 mg q2w vs placebo
	Change from baseline in TSS at Week 24	
	Change from baseline in smell test (UPSIT) at Week 24	
	Change from baseline in loss of smell daily symptoms at Week 24	
	Change from baseline in SNOT-22 at Week 24	

a In addition to the key secondary endpoints listed, 2 pre-specified analyses based on pooled data from Study EFC14280 and EFC14146 were included in the hierarchy: Proportion of patients requiring rescue with SCS or NP surgery and FEV_1 at Week 24. The results of the pooled analyses are provided in 2.7.3 Summary of Clinical Efficacy.

b Change from baseline in LMK score was a coprimary endpoint and was not a key secondary endpoint in Japan.

Results (study EFC14146)

Participant flow



506 patients were screened of which 230 (45.5%) were classified as screen failures. The leading reasons for screen failure were failure to meet the inclusion criterion of a minimum score of 5 points on the bilateral NPS (22.7%), failure to meet the inclusion criteria for ongoing symptoms with a NC score of 2 or 3 and another symptom (6.1%), and noncompliance with the NIMP at Visit

2 (5.9%). Of the remaining 276 patients, 143 patients were randomized to dupilumab 300 mg q2w and 133 were randomized to placebo. Overall, 263 patients completed 24 weeks of study treatment. Twelve (4.3%) patients discontinued from the study treatment prior to Week 24 and 1 patient did not receive any study treatment. In general, study treatment discontinuation rates were higher in the placebo group (5.3%) compared to the dupilumab group (3.5%) with AEs as primary reason for discontinuation. Treatment exposure was similar between treatment groups, with a mean exposure of 164.56 days in the dupilumab group versus 163.39 days in the placebo group.

There were 10 (7.0%) and 25 (18.8%) patients with first rescue with either SCS or surgery prior to Week 24 in the dupilumab group and the placebo group, respectively.

Patients disposition - Randomized population

	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Randomized and not treated	0	1 (0.7%)
Not treated per patient's request	0	0
Randomized and treated	133 (100%)	142 (99.3%)
Completed study treatment during the 24-week treatment period	126 (94.7%)	137 (95.8%)
Discontinued study treatment during the 24-week treatment period	7 (5.3%)	5 (3.5%)
Study treatment discontinuation prior to Week 24 per patient's request	5 (3.8%)	1 (0.7%)
Reason for study treatment discontinuation prior to Week 24		
Adverse event	3 (2.3%)	5 (3.5%)
Lack of efficacy	1 (0.8%)	0
Poor compliance to protocol	0	0
Other reason	3 (2.3%)	0
Patients with first SCS/surgery prior to Week 24 (study day 169)	25 (18.8%)	10 (7.0%)
Completed the 24-week study period	130 (97.7%)	141 (98.6%)
Discontinued from the study prior to Week 24	3 (2.3%)	1 (0.7%)
Reason for study discontinuation prior to Week 24		
Adverse event	1 (0.8%)	1 (0.7%)
Poor compliance to protocol	0	0
Study terminated by sponsor	0	0
Other reason	2 (1.5%)	0
Completed the study period	124 (93.2%)	138 (96.5%)
Discontinued from the study period	9 (6.8%)	4 (2.8%)
Reason for study discontinuation		
Adverse event	3 (2.3%)	2 (1.4%)
Poor compliance to protocol	0	0
Study terminated by sponsor	0	0
Other reason	6 (4.5%)	2 (1.4%)
Status at last study contact		
Alive	132 (99.2%)	142 (99.3%)
Dead	1 (0.8%)	0

Note: percentages are calculated using the number of patients randomized as denominator
PGM=PRODOPS/SAR231893/EFC14146/CSR/REPORT/PGM/dis_dispo_r_t.sas OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (02DEC2018 - 2:49)

Recruitment

Study Initiation Date (first patient enrolled): 05 December 2016

Study Completion Date (last patient last visit): 05 July 2018

Conduct of the study

Protocol deviations

29.4% of patients in the dupilumab group and 42.9% of patients in the placebo group had a deviation considered critical or major. The most frequently occurring of these deviations were deviations in the schedule of assessments or procedures (eg, a study visit or phone call not performed or performed outside of the visit window) occurring in 21.0% and 33.1% of patients in the dupilumab and placebo groups, respectively and deviations in IMP management (eg, missed IMP dose, or IMP administered but not per protocol) occurring in 7.0% and 9.8% of patient in the dupilumab and placebo groups, respectively.

A subset of critical or major deviations that could potentially impact efficacy analyses were identified. These included failure to meet the inclusion criteria or violation of exclusion criteria related to the co-primary efficacy endpoints, use of prohibited concomitant medications that interfere with the primary analysis approach on SCS rescue, missing co-primary efficacy endpoint assessments, or noncompliance or randomization procedures that result in <80% compliance with the IMP). These critical or major deviations that could potentially impact the efficacy analyses were reported for a small percentage of patients in both the dupilumab and placebo groups (3.5% versus 3.0%, respectively).

The most common type of major protocol deviations potentially impacting efficacy analyses was the allowance of a patient to stay in the study until after Week 24 even with a missing NC score between Weeks 21 and 24 (reported in 2 patients [1.4%] in the dupilumab group versus 3 patients [2.3%] in the placebo group). The second most common type of major protocol deviations potentially impacting efficacy analyses was failure to meet the inclusion criterion requiring ongoing symptoms for at least 8 weeks before randomization (reported in 2 patients [1.4%] in the dupilumab group and 1 patient [0.8%] in the placebo group). The critical/major protocol deviations potentially impacting efficacy were observed across all treatment groups, with no apparent distribution pattern.

Deviation categories n(%)	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Any major or critical deviations potentially impacting efficacy analyses	4 (3.0%)	5 (3.5%)
Inclusion/Exclusion Criteria	1 (0.8%)	2 (1.4%)
I02: Ongoing symptoms (for at least 8 weeks before V1) of: - Nasal congestion score 2 or 3 at V1 and a weekly average of > 1 at V2. AND - Another symptom: loss of smell, rhinorrhea (anterior/posterior).	1 (0.8%)	2 (1.4%)
Concomitant Medications/Therapy	1 (0.8%)	1 (0.7%)
Short course courses (<=2 weeks) of OCS only between V1 and V2.	1 (0.8%)	0
Administration of other monoclonal antibody	0	1 (0.7%)
Any systemic immunosupressive treatment including methotrexate, cyclosporine, mycophenolate, tacrilomus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide.	0	1 (0.7%)
Assessments/Procedures	3 (2.3%)	2 (1.4%)
Missing NC score date from week 21 to week 24 and stay in the study until after Week 24	3 (2.3%)	2 (1.4%)
IMP Management	1 (0.8%)	0
IMP administered but not as per protocol Note: it includes e.g. route, site,dosage, etc and Treatment compliance < 80%	1 (0.8%)	0

Note: Percentages are calculated using the number of patients randomized as denominator
PGM=PRODOPS/SAR231893/EFC14146/CSR/EXPLO/PGM/a_dev_summary_r_t.sas
OUT=EXPLO/OUTPUT/a_dev_other_important1_r_t_i.rtf (10DEC2018 - 4:19)

Changes in the conduct of the study

One global amendment was made to the study protocol for the purpose of clarifying and correcting several points in the protocol that may have been insufficiently explained.

Table: Summary of protocol amendments- Study EFC14146

Date	Purpose of amendments
17 May 2017	• Clarification of early treatment discontinuation language • Restesting of dynamic laboratory values during screening • Analysis changed to systemic corticosteroids from oral corticosteroids • EQ-5D elevated from exploratory endpoint to secondary endpoint • Clarified CT scan administration to be mandatory unless not approved by local ethics committee or IRB • Intranasal decongestants added to list of prohibited medications except as needed for nasal endoscopy procedure • Study procedures can be performed over 3 days if necessary as long as the visit window is respected • Updated safety language throughout the protocol to be consistent with most current safety information per latest investigators brochure: Male birth control no longer required • Clarified that rescue therapy prescribed by the investigator will not be provided by the Sponsor

Changes in the planned analyses:

Table: From the statistical analysis plan to database lock- Study EFC14146

Text in SAP	Description of changes in CSR	Rational of change
The following item in Section 2.1.1 demographic characteristics • Weight in kg (quantitative and qualitative variable : <50, 50-<100 and ≥100 kg)	is changed to • Weight in kg (quantitative and qualitative variable : <70, >=70-<90, >= 90kg)	Revised to more appropriate categories for subgroup analysis
The following wording in adverse events of special interest and other selected AE groupings criteria for anaphylactic reaction • Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple symptoms, the symptoms must have occurred within 24 hours of each other	Is changed to • Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.	Revised to add medical review process for the programmatic identified cases.
The following criteria for epistaxis/nose bleeding in adverse events of special interest and other selected AE groupings • PT in (Epistaxis, Nasal septum haematoma)	is changed to • PT in (Epistaxis)	Revised to more scientifically appropriate term.
The following wording in adverse events of special interest and other selected AE groupings • Hypereosinophilia	is changed to • Eosinophilia	Revised to more scientifically appropriate term.
The following statement in efficacy analysis regarding primary approach • For patients who discontinue the treatment without being rescued by surgery or receiving SCS, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all patients who have not been rescued by surgery or receiving SCS at Week 24.	is changed to • Patients who discontinue the treatment without being rescued by surgery or receiving SCS are encouraged to follow the planned clinical visits, and all data collected after treatment discontinuation will be used in the analysis. For these patients, because missing data may still happen despite all efforts have been tried to collect the data after treatment discontinuation, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all patients who have not been rescued by surgery or receiving SCS at Week 24.	To make further clarifications according to FDA's comment
Section 2.4.5.5 Analysis of electrocardiogram variables	Is revised to The incidence of normal/abnormal at any time post-baseline will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories: • Normal/missing • Abnormal	To be aligned with collection for electrocardiogram data

Text in SAP	Description of changes in CSR	Rational of change
In Section 2.5.2 Periodical average of daily efficacy endpoints at designated study days	Additional 4-week averages time points (day 85, 141, 197, 225, 281, 309) are added in Table 2 Periodical average of daily efficacy assessment for every 4 weeks from Day 29 (average of study days 2-29) to Day 337 (average of study days 310-337) or Day 169 (NPIF only, average of study days 142-169).	To assess daily efficacy endpoints for every 4 weeks

Similar protocol amendments and changes in the planned analyses were made in both studies. These changes were unlikely to have a significant impact on the study results. In both studies a number of patients had a deviation considered critical or major (Study EFC14146: 29.4% of patients in the dupilumab group and 42.9% of patients in the placebo group, Study EFC14280: 38.7% of patients in the dupilumab 300 mg q2w group, 40.7% of patients in the 300 mg q2w-q4w group, and 49.7% of patients in the placebo group).

Baseline data

The mean time since first diagnosis of CRSwNP was 11.11 years and ranged from 0.2 to 42.5 years. Baseline mean NPS of 5.75 (out of maximum of 8), mean NC severity score of 2.35 (out of a maximum score of 3), mean SNOT-22 total score of 49.4 (out of maximum possible score of 110), mean UPSIT score of 14.56 (indicating anosmia [score of 0 to 18, out of a maximum score of 39]), and mean TSS of 7.04 (out of a maximum score of 9) are suitable for patients with severe CRSwNP. CT-scan evaluation demonstrated that most patients had extensive opacification of the sinuses bilaterally as assessed by the CT scan LMK total mean score of 19.03 (maximum possible score of 24). 73% of the patients had at least partial opacification of all sinuses. The mean VAS for rhinosinusitis was 7.68 (severe disease >7 to 10) and mean loss of smell at baseline of 2.71 (maximum score of 3).

Demographics and patient characteristics at baseline - Randomized population

	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	All (N=276)
Age (years)			
Number	133	143	276
Mean (SD)	50.83 (13.21)	50.17 (13.59)	50.49 (13.39)
Median	50.00	52.00	51.00
Q1 : Q3	41.00 : 60.00	39.00 : 61.00	40.00 : 60.00
Min : Max	22.0 : 85.0	23.0 : 79.0	22.0 : 85.0
Age group (years) [n (%)]			
Number	133	143	276
18 - 64	112 (84.2%)	121 (84.6%)	233 (84.4%)
65 - 74	15 (11.3%)	18 (12.6%)	33 (12.0%)
75 - 84	5 (3.8%)	4 (2.8%)	9 (3.3%)
≥ 85	1 (0.8%)	0	1 (0.4%)
Sex [n (%)]			
Number	133	143	276
Male	70 (52.6%)	88 (61.5%)	158 (57.2%)
Female	63 (47.4%)	55 (38.5%)	118 (42.8%)
Region[a] [n (%)]			
Number	133	143	276
East Europe	86 (64.7%)	87 (60.8%)	173 (62.7%)
Western Countries	47 (35.3%)	56 (39.2%)	103 (37.3%)
Territory[b] [n (%)]			
Number	133	143	276
North America	16 (12.0%)	18 (12.6%)	34 (12.3%)
European Union	85 (63.9%)	92 (64.3%)	177 (64.1%)
Rest of World	32 (24.1%)	33 (23.1%)	65 (23.6%)
Race [n (%)]			
Number	133	143	276
Caucasian/White	126 (94.7%)	138 (96.5%)	264 (95.7%)
Black/of African descent	7 (5.3%)	2 (1.4%)	9 (3.3%)
Asian/Oriental	0	1 (0.7%)	1 (0.4%)
Japanese	0	0	0
American Indian or Alaska Native	0	1 (0.7%)	1 (0.4%)
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple	0	0	0
Unknown	0	1 (0.7%)	1 (0.4%)
Weight (kg)			
Number	133	143	276
Mean (SD)	82.44 (19.35)	81.56 (17.89)	81.98 (18.58)
Median	80.00	79.40	80.00
Q1 : Q3	69.00 : 93.60	70.00 : 95.20	69.45 : 95.00
Min : Max	48.0 : 156.3	38.0 : 130.0	38.0 : 156.3
Weight group (kg) [n (%)]			
Number	133	143	276
< 70	35 (26.3%)	35 (24.5%)	70 (25.4%)
≥ 70 - < 90	55 (41.4%)	59 (41.3%)	114 (41.3%)
≥ 90	43 (32.3%)	49 (34.3%)	92 (33.3%)

Body mass index (BMI) (kg/m^2)			
Number	133	143	276
Mean (SD)	28.36 (5.76)	27.49 (5.11)	27.91 (5.44)
Median	26.87	26.84	26.87
Q1 : Q3	24.37 : 31.89	23.94 : 31.07	24.27 : 31.11
Min : Max	18.4 : 45.0	16.4 : 41.7	16.4 : 45.0
BMI group (kg/m^2) [n (%)]			
Number	133	143	276
< 25	47 (35.3%)	50 (35.0%)	97 (35.1%)
≥ 25 - < 30	46 (34.6%)	48 (33.6%)	94 (34.1%)
≥ 30	40 (30.1%)	45 (31.5%)	85 (30.8%)
Smoking history [n(%)]			
Number	133	143	276
Former	33 (24.8%)	38 (26.6%)	71 (25.7%)
Current	14 (10.5%)	14 (9.8%)	28 (10.1%)
Never	86 (64.7%)	91 (63.6%)	177 (64.1%)
Cessation prior to screening (months)			
Number	33	36	69
Mean (SD)	167.85 (145.38)	208.56 (164.36)	189.09 (155.79)
Median	135.00	196.50	150.00
Q1 : Q3	29.00 : 258.00	67.50 : 303.50	63.00 : 302.00
Min : Max	5.0 : 486.0	2.0 : 594.0	2.0 : 594.0
Pack-year			
Number	45	48	93
Mean (SD)	16.82 (22.39)	12.33 (19.82)	14.50 (21.11)
Median	12.60	5.00	7.50
Q1 : Q3	5.00 : 22.50	1.50 : 18.25	3.00 : 20.00
Min : Max	0.1 : 148.0	0.0 : 120.0	0.0 : 148.0
Frequency of alcohol drinking in the past 12 months [n(%)]			
Number	133	143	276
Never	45 (33.8%)	42 (29.4%)	87 (31.5%)
Occasional	56 (42.1%)	70 (49.0%)	126 (45.7%)
At least monthly	10 (7.5%)	15 (10.5%)	25 (9.1%)
At least weekly	19 (14.3%)	12 (8.4%)	31 (11.2%)
At least daily	3 (2.3%)	4 (2.8%)	7 (2.5%)

In the 2 years prior to randomization, 179 (64.9%) patients received at least one course of SCS. 71.7% patients had a sino-nasal surgery prior to randomization. Of these, 45.5% had 1 surgery and 54.5% of patients had 2 or more previous surgeries. The mean time since the most recent sino-nasal surgery was 5.74 years (ranging from 0.6 to 34.5 years). 58.3% had a medical history of asthma and 30.4% patients had a history of NSAID-ERD. 88.8% of the patients with asthma were on asthma medication in the prior year and 76.7% were using ICS and LABA. 75.4% had a medical history of at least 1 type 2 inflammation mediated disease. The incidence of patients with each type 2 inflammation mediated comorbidities was similar among treatment groups.

Summary of history of prior NP surgery, systemic corticosteroid use, and epistaxis - Randomized population

	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	All (N=276)
Time since first diagnosis of nasal polyposis (years)			
Number	133	143	276
Mean (SD)	10.77 (8.57)	11.42 (9.69)	11.11 (9.16)
Median	9.49	9.68	9.53
Q1 : Q3	4.25 : 15.47	3.26 : 17.27	3.45 : 15.56
Min : Max	0.2 : 37.5	0.3 : 42.5	0.2 : 42.5
Age of onset of nasal polyposis (years)			
Number	133	143	276
Mean (SD)	40.17 (13.07)	38.83 (13.90)	39.48 (13.50)
Median	39.00	38.00	39.00
Q1 : Q3	29.00 : 50.00	27.00 : 50.00	29.00 : 50.00
Min : Max	15.0 : 79.0	11.0 : 73.0	11.0 : 79.0
Number of patients with prior surgery from IVRS	100 (75.2%)	102 (71.3%)	202 (73.2%)
Number of patients with prior surgery for nasal polyposis and/or SCS use during the past 2 years	130 (97.7%)	141 (98.6%)	271 (98.2%)
Number of patients with prior surgery for nasal polyposis	99 (74.4%)	99 (69.2%)	198 (71.7%)
Number of previous surgeries for nasal polyposis			
Number[a]	99 (74.4%)	99 (69.2%)	198 (71.7%)
Mean (SD)	2.13 (1.50)	2.34 (1.93)	2.24 (1.73)
Median	2.00	2.00	2.00
Q1 : Q3	1.00 : 3.00	1.00 : 3.00	1.00 : 3.00
Min : Max	1.0 : 8.0	1.0 : 11.0	1.0 : 11.0
1	45 (45.5%)	45 (45.5%)	90 (45.5%)
2	25 (25.3%)	21 (21.2%)	46 (23.2%)
≥3	29 (29.3%)	33 (33.3%)	62 (31.3%)

Number of patients with SCS use during the past 2 years	87 (65.4%)	92 (64.3%)	179 (64.9%)
Number of courses[b] with SCS use during the past 2 years			
Number[c]	87 (65.4%)	92 (64.3%)	179 (64.9%)
Mean (SD)	1.45 (0.85)	1.43 (0.83)	1.44 (0.84)
Median	1.00	1.00	1.00
Q1 : Q3	1.00 : 2.00	1.00 : 2.00	1.00 : 2.00
Min : Max	1.0 : 5.0	1.0 : 6.0	1.0 : 6.0
1	63 (72.4%)	65 (70.7%)	128 (71.5%)
2	13 (14.9%)	18 (19.6%)	31 (17.3%)
3	8 (9.2%)	7 (7.6%)	15 (8.4%)
4	2 (2.3%)	1 (1.1%)	3 (1.7%)
≥5	1 (1.1%)	1 (1.1%)	2 (1.1%)
Number of days with SCS use during the past 2 years			
Number[d]	55 (41.4%)	62 (43.4%)	117 (42.4%)
Mean (SD)	14.20 (13.31)	14.66 (17.70)	14.44 (15.72)
Median	10.00	10.00	10.00
Q1 : Q3	6.00 : 15.00	7.00 : 16.00	7.00 : 15.00
Min : Max	1.0 : 60.0	2.0 : 135.0	1.0 : 135.0
Number[e]	87 (65.4%)	92 (64.3%)	179 (64.9%)
>0-≤7	18/87 (20.7%)	17/92 (18.5%)	35/179 (19.6%)
>7-≤14	23/87 (26.4%)	25/92 (27.2%)	48/179 (26.8%)
>14-≤21	5/87 (5.7%)	12/92 (13.0%)	17/179 (9.5%)
>21-≤28	2/87 (2.3%)	3/92 (3.3%)	5/179 (2.8%)
>28-≤56	5/87 (5.7%)	4/92 (4.3%)	9/179 (5.0%)
>56-≤84	2/87 (2.3%)	0/92	2/179 (1.1%)
>84-≤112	0/87	0/92	0/179
>112	8/87 (9.2%)	6/92 (6.5%)	14/179 (7.8%)
Undetermined duration	24/87 (27.6%)	25/92 (27.2%)	49/179 (27.4%)
Epistaxis history			
Number	133	143	276
Yes	9 (6.8%)	18 (12.6%)	27 (9.8%)
Ongoing	4 (3.0%)	10 (7.0%)	14 (5.1%)

SCS: systemic corticosteroid

a Number of patients with at least 1 previous surgery

b A course of SCS is considered continuous if treatment is separated by less than 7 days.

c Number of patients who used at least one course of SCS

d Number of patients with >= 1 day of SCS use and complete dates reported

e Number of patients with >= 1 day of SCS use

The demographic and baseline characteristics were generally similar between dupilumab and placebo groups. Overall, the literature suggests that CRSwNP increases with age, with a mean onset across all ethnic groups of 42 years. CRSwNP is uncommon under the age of 20 years and occurs more frequently in men than in women; aspirin-sensitive patients, however, are more likely to be women.

Numbers analysed

	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	All (N=276)
Randomized population	133 (100%)	143 (100%)	276 (100%)
Efficacy population			
Intent-to-Treat (ITT)	133 (100%)	143 (100%)	276 (100%)
Safety population	132	143	275
PK population	0	142	142
ADA population	132	143	275

Outcomes and estimation

Study EFC14146: Summary of results for all endpoints in the hierarchical testing procedure

	Placebo (N=133)			Dupilumab 300mg q2w (N=143)				
	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Absolute Difference for Dupilumab vs. Placebo LS Mean (95% CI)	P Value
Primary endpoints								
Bilateral nasal polyps score (NPS) at Week 24	5.86 (1.31)	5.94 (1.44)	0.17 (0.15)	5.64 (1.23)	3.75 (1.98)	-1.89 (0.14)	-2.06 (-2.43, -1.69)	<.0001
Nasal congestion/obstruction (NC) at Week 24	2.45 (0.55)	1.90 (0.85)	-0.45 (0.07)	2.26 (0.57)	0.94 (0.75)	-1.34 (0.07)	-0.89 (-1.07, -0.71)	<.0001
Key secondary endpoints								
Lund Mackay score (LMK) at Week 24	19.55 (4.26)	18.97 (4.51)	-0.74 (0.37)	18.55 (4.55)	10.89 (4.82)	-8.18 (0.34)	-7.44 (-8.35, -6.53)	<.0001
Total symptom score (TSS) at Week 24	7.28 (1.40)	6.02 (2.02)	-1.17 (0.17)	6.82 (1.35)	3.16 (1.93)	-3.77 (0.16)	-2.61 (-3.04, -2.17)	<.0001
Smell test (UPSIT) at Week 24	14.44 (8.31)	14.56 (8.58)	0.70 (0.71)	14.68 (8.66)	25.39 (9.49)	11.26 (0.67)	10.56 (8.79, 12.34)	<.0001
Loss of smell at Week 24	2.73 (0.51)	2.50 (0.77)	-0.29 (0.07)	2.70 (0.57)	1.35 (0.99)	-1.41 (0.07)	-1.12 (-1.31, -0.93)	<.0001
SNOT-22 total score at Week 24	50.87 (20.22)	40.49 (23.06)	-9.31 (1.62)	48.00 (20.16)	18.58 (14.92)	-30.43 (1.54)	-21.12 (-25.17, -17.06)	<.0001

PGM=DEVOPS/SAR231893/EFC14146/CSR/REPORT/PGM/eff_hierarchical_test_i_t.sas OUT=REPORT/OUTPUT/eff_hierarchical_test_i_t_i.rtf (01DEC2018 - 20:02)
Note: The ranges of possible scores for each endpoint were as follows, with the highest score representing most severe disease: NPS (0 to 8), NC score (0 to 3), LMK (0 to 24), TSS (0 to 9), loss of smell (0 to 3), SNOT-22 total score (0 to 110, with an MCID of 8.9). The range for the UPSIT was 0 to 40 (with lowest score representing most severe loss of smell and scores ≤18 classified as anosmia).
A reduction in score indicates improvement, except UPSIT where an increase indicates improvement.

CO-PRIMARY EFFICACY ENDPOINTS

- **CHANGE FROM BASELINE IN NASAL POLYPOSIS SCORE (NPS)**

Primary analysis: Change from baseline in nasal polyps score at Week 24

Dupilumab 300 mg q2w demonstrated a statistically significant improvement in mean bilateral endoscopic NPS compared with placebo at Week 24, with an LS mean change from baseline to Week 24 of -1.89 for 300 mg q2w dupilumab and +0.17 for placebo (LS mean difference versus placebo: -2.06 with 95% CI: -2.43 to -1.69 ($p<0.0001$).

Primary approach: change from baseline in bilateral nasal polyps score (NPS) at Week 24 - ITT population

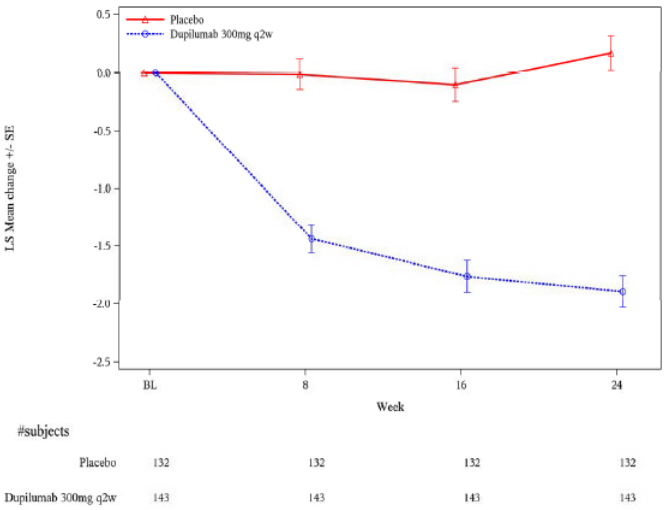
NPS	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Baseline		
Number	132	143
Mean (SD)	5.86 (1.31)	5.64 (1.23)
Median	6.00	5.50
Q1 : Q3	5.00 : 7.00	5.00 : 6.00
Min : Max	2.0 : 8.0	2.0 : 8.0
Week 24		
Number	128	137
Mean (SD)	5.94 (1.44)	3.75 (1.98)
Median	6.00	4.00
Q1 : Q3	5.00 : 7.00	2.50 : 5.00
Min : Max	1.0 : 8.0	0.0 : 8.0
Change from baseline		
Number	128	137
Mean (SD)	0.11 (1.28)	-1.88 (1.83)
Median	0.00	-1.50
Q1 : Q3	-0.50 : 0.75	-3.00 : -0.50
Min : Max	-5.0 : 4.0	-6.5 : 3.0
LS Mean (SE) [a]	0.17 (0.15)	-1.89 (0.14)
LS Mean Diff vs. placebo (95% CI) [a]		-2.06 (-2.43, -1.69)
P-value vs. placebo [a]		<.0001

a Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.

Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis

An improvement in NPS was observed as early as the first post-baseline assessment at Week 8 with an LS mean difference in the dupilumab group versus placebo of -1.42 with 95% CI: -1.75 to -1.10 (nominal p <0.0001). The improvement in NPS continued through week 24.

LS mean change from baseline in bilateral nasal polyps score (NPS) by visit up to Week 24 - ITT population



Sensitivity analyses of change from baseline in nasal polyposis score at Week 24

The results of the MMRM analyses of the change from baseline in bilateral NPS at Week 24 were similar to those of the primary WOCF/MI analysis. The LS mean difference in the dupilumab group versus placebo was -2.13 with 95% CI: -2.52 to -1.73 (p<0.0001).

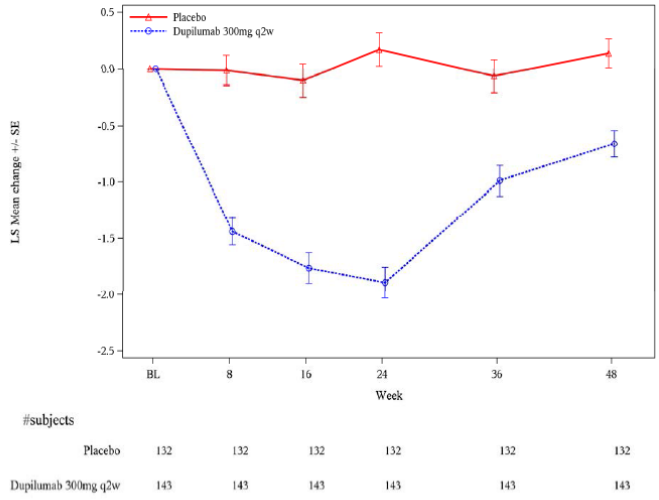
The PMM analyses of the change from baseline in bilateral NPS at Week 24 demonstrated results similar to those of the primary WOCF/MI analysis. The LS mean difference in the dupilumab group versus placebo was -2.01 with 95% CI: -2.41 to -1.61 (p<0.0001).

The results of the as-observed analyses of the change from baseline in bilateral NPS at Week 24 demonstrated similar to those of the primary WOCF/MI analysis. The LS mean difference in the dupilumab group vs placebo was -1.98 with 95% CI: -2.35 to -1.61 (p<0.0001).

Analysis through the 24-week follow-up period

During the follow up period, the treatment effect in NPS between Week 24 to Week 48 diminished without rebound in the dupilumab group after treatment discontinuation, with an LS mean difference versus placebo of -0.92 at Week 36 and -0.80 at Week 48 from baseline.

LS mean change from baseline in bilateral nasal polyps score (NPS) by visit up to Week 48 - ITT population



Responder Analysis at Week 24

A higher percentage of patients had a ≥1 point improvement in NPS in the dupilumab group compared with the placebo (65.0% versus 17.3%, nominal p<0.0001). Similarly, the proportion of patients showing a ≥2 points improvement in NPS was greater in the dupilumab group compared with the placebo group (46.2 % versus 4.5%, nominal p<0.0001).

- **CHANGE FROM BASELINE IN NASAL CONGESTION/OBSTRUCTION (NC)**

Nasal congestion/obstruction was assessed by the patient daily basis using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) as a reflective assessment using a 24-hour recall period.

Primary analysis: Change from baseline in nasal congestion/obstruction at Week 24

A statistically significant improvement in the mean NC symptom score in favour of dupilumab 300 mg q2w compared with placebo is seen at Week 24. The LS mean change from baseline to Week 24 was -1.34 for the dupilumab group and -0.45 for the placebo group (LS mean difference versus placebo: -0.89 with 95% CI: -1.07 to -0.71; p<0.0001).

Primary approach: Change from baseline in nasal congestion/obstruction (NC) at Week 24 - ITT population

NC	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Baseline		
Number	133	143
Mean (SD)	2.45 (0.55)	2.26 (0.57)
Median	2.57	2.00
Q1 : Q3	2.00 : 3.00	2.00 : 3.00
Min : Max	1.1 : 3.0	1.0 : 3.0
Week 24		
Number	130	141
Mean (SD)	1.90 (0.85)	0.94 (0.75)
Median	2.00	1.00
Q1 : Q3	1.27 : 2.86	0.24 : 1.19
Min : Max	0.0 : 3.0	0.0 : 3.0
Change from baseline		
Number	130	141
Mean (SD)	-0.54 (0.79)	-1.33 (0.80)
Median	-0.33	-1.24
Q1 : Q3	-1.00 : 0.00	-2.00 : -0.86
Min : Max	-3.0 : 1.3	-3.0 : 0.1
LS Mean (SE) [a]	-0.45 (0.07)	-1.34 (0.07)
LS Mean Diff vs. placebo (95% CI) [a]		-0.89 (-1.07, -0.71)
P-value vs. placebo [a]		<.0001

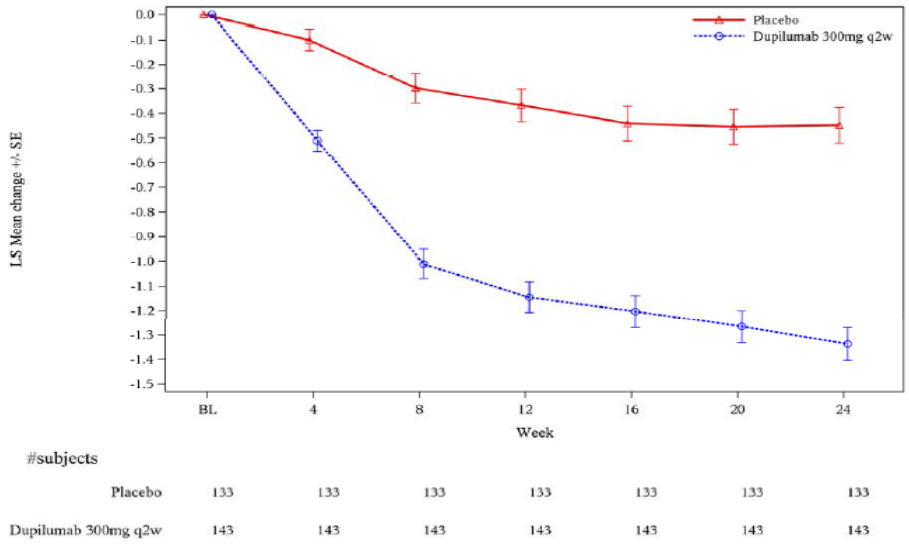
a Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.

Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis

PGM=PRODOPS/SAR231893/EFC14146/CSR/REPORT/PGM/eff_ancova_i_t.sas OUT=REPORT/OUTPUT/eff_ancova_nc_wk24_i_t_i.rtf (01DEC2018 - 13:58)

A rapid onset of improvement was seen with a significant difference versus placebo as early as the first post-baseline monthly average score at Week 4 with an LS mean change from baseline to Week 4 of -0.51 for the dupilumab group and -0.10 for the placebo group (LS mean difference versus placebo: -0.41 with 95% CI: -0.52 to -0.30; p<0.0001).

LS mean change from baseline in nasal congestion/obstruction (NC) by month up to Week 24 - ITT population



#subjects							
Placebo	133	133	133	133	133	133	133
Dupilumab 300mg q2w	143	143	143	143	143	143	143

The improvement in NC symptom continued through Week 24.

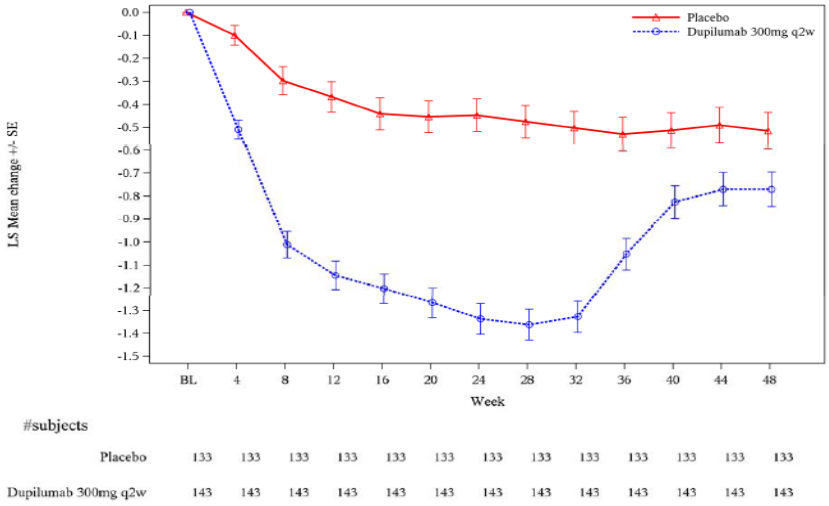
Sensitivity analyses

Results of the MMRM analyses of the change from baseline in NC at Week 24 were similar to those of the primary WOCF/MI analysis. The LS mean difference in the dupilumab group versus placebo was -0.88 with 95% CI: -1.05 to -0.70 (p<0.0001). The results of the PMM analyses of the change from baseline in NC at Week 24 were also similar to those of the primary WOCF/MI analysis as well as the as-observed analyses of the change from baseline in NC at Week 24.

Analysis through the 24-week follow-up period

During the 24-week follow up period, NC treatment effect diminished without rebound in the dupilumab group after treatment discontinuation, with an LS mean difference versus placebo of -0.52 at Week 36 and -0.26 at Week 48 from baseline

LS mean change from baseline in nasal congestion/obstruction (NC) by month up to Week 48- ITT population



KEY SECONDARY EFFICACY ENDPOINTS

- **Sinus opacification CT scan score (Lund-Mackay score)**

A range of staging systems for CT scanning have been described, the most commonly used being the Lund-Mackay system. This system relies on a score of 0–2 dependent on the absence, partial, or complete opacification of each sinus system and of the vital ostiomeatal complex deriving a maximum score of 12 per side. This has been validated but the correlation between the CT score and symptoms has been shown to be poor and is not a good indicator of outcome.

Change from baseline to Week 24 (Multiplicity controlled)

The dupilumab 300 mg q2w group showed a statistically significant improvement in the mean sinus opacification CT scan score (LMK) compared with placebo receiving INCS who showed minimal changes in sinus disease at Week 24 (LS mean difference in the dupilumab group versus placebo: -7.44 with 95% CI: -8.35 to -6.53; p<0.0001).

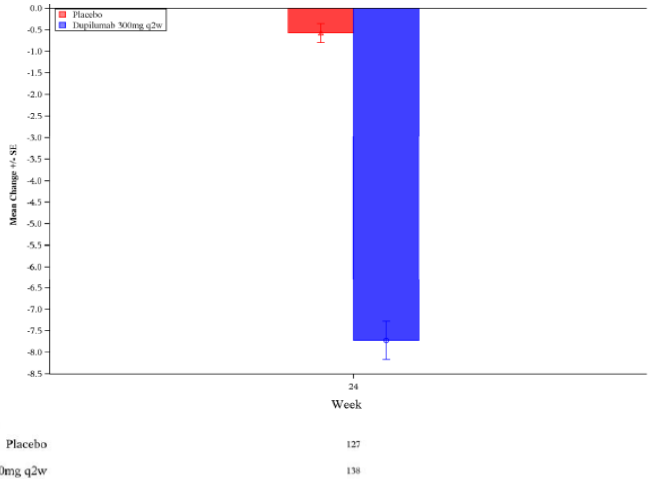
Primary approach: change from baseline in sinus opacification CT scan score (Lund-Mackay score) at Week 24 - ITT population

LMK	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Baseline		
Number	129	141
Mean (SD)	19.55 (4.26)	18.55 (4.55)
Median	21.00	20.00
Q1 : Q3	17.00 : 23.00	15.00 : 22.00
Min : Max	6.0 : 24.0	4.0 : 24.0
Week 24		
Number	127	138
Mean (SD)	18.97 (4.51)	10.89 (4.82)
Median	20.00	10.50
Q1 : Q3	15.00 : 23.00	8.00 : 14.00
Min : Max	7.0 : 24.0	0.0 : 24.0
Change from baseline		
Number	127	138
Mean (SD)	-0.57 (2.48)	-7.72 (5.20)
Median	0.00	-8.00
Q1 : Q3	-2.00 : 1.00	-11.00 : -4.00
Min : Max	-11.0 : 5.0	-19.0 : 4.0
LS Mean (SE) [a]	-0.74 (0.37)	-8.18 (0.34)
LS Mean Diff vs. placebo (95% CI) [a]		-7.44 (-8.35, -6.53)
P-value vs. placebo [a]		<.0001

a Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.

Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis

Mean change from baseline in sinus opacification CT scan score (Lund-Mackay score) by visit up to Week 24 - ITT population



Change from baseline to Week 24 on left and right side and by individual sinus

Dupilumab 300 mg q2w demonstrated improvements in mean sinus opacification CT scan score (LMK) from baseline to Week 24 on both the left and right sides compared with the placebo (LS mean difference versus placebo [95% CI] was -3.56 [-4.06 to -3.06] for the left side and -3.92 [-4.41 to -3.42] for the right side; nominal p<0.0001 for each side. Consistent with its systemic effect in the type 2 inflammation, dupilumab demonstrated improvements in mean sinus opacification CT scan score (LMK) compared with placebo at Week 24 across all individual sinuses bilaterally, indicating that the effect of dupilumab in total LMK score was obtained through reduction of the inflammation in multiple sinuses and was not only driven by the shrinkage of the polyps in the nasal cavity.

The results for the sensitivity analyses were similar to those of the primary WOCF/MI analysis.

Analysis through the 24-week follow-up period

During the follow up period, treatment effect in sinus opacification CT scan score (LMK) diminished without rebound in the dupilumab group after treatment discontinuation, with an LS mean difference versus placebo of -1.79 at Week 48.

- **Disease specific daily symptom assessment and total symptom score (TSS)**

The TSS is a composite score consisting of the sum of the symptoms scores for NC, decreased/loss of sense of smell, and rhinorrhea on a 0-3 scale (maximum of 9).

Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab displayed a statistically significant improvement in mean TSS compared with placebo at Week 24 (LS mean difference in the dupilumab group versus placebo: -2.61 with 95% CI: -3.04 to -2.17; p<0.0001).

Change from baseline in TSS at Week 24 - ITT population

TSS	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Baseline		
Number	133	143
Mean (SD)	7.28 (1.40)	6.82 (1.35)
Median	7.43	7.00
Q1 : Q3	6.00 : 8.50	6.00 : 7.86
Min : Max	2.3 : 9.0	2.8 : 9.0
Week 24		
Number	129	141
Mean (SD)	6.02 (2.02)	3.16 (1.93)
Median	6.08	3.04
Q1 : Q3	4.81 : 7.63	2.00 : 4.07
Min : Max	0.0 : 9.0	0.0 : 9.0
Change from baseline		
Number	129	141
Mean (SD)	-1.26 (1.71)	-3.69 (2.04)
Median	-1.02	-3.87
Q1 : Q3	-2.36 : 0.00	-5.00 : -2.21
Min : Max	-5.9 : 1.6	-8.9 : 0.8
LS Mean (SE) [a]	-1.17 (0.17)	-3.77 (0.16)
LS Mean Diff vs. placebo (95% CI) [a]		-2.61 (-3.04, -2.17)
P-value vs. placebo [a]		<.0001

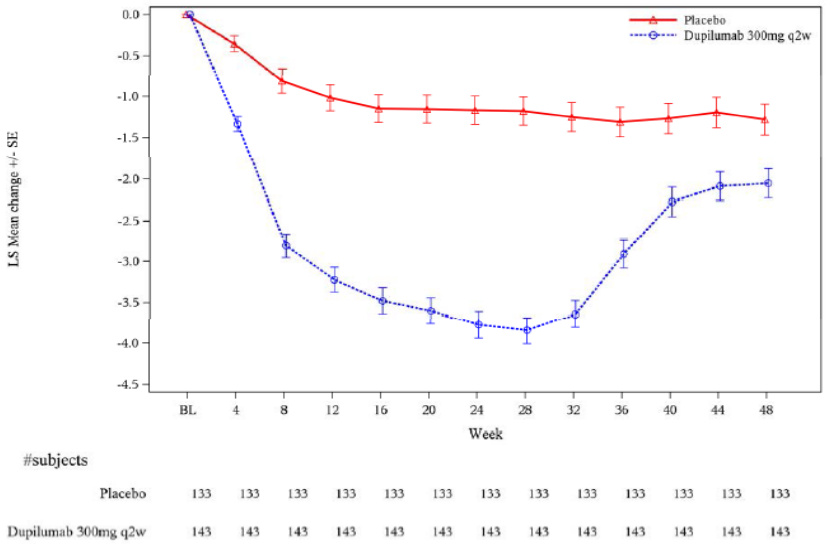
a Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.

Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

The improvement in TSS score was rapid with an onset of a difference vs placebo observed as early as the first post-baseline monthly average score at Week 4 with an LS mean change from baseline to Week 4 of -1.34 for the dupilumab group and -0.35 for the placebo group (LS mean difference versus placebo: -0.98 with 95% CI: -1.22 to -0.74; p<0.0001).

Analysis through 24-week follow-up

During the 24 week off-treatment follow up period, the improvement in the TSS diminished without rebound in the dupilumab group after treatment discontinuation, with an LS mean difference versus placebo of -1.60 at Week 36 and -0.77 at Week 48.



- **Smell test: University of Pennsylvania Smell Identification Test (UPSIT)**

The UPSIT was 40 odorant test administered at the study site. Each patient received a score ranging from 0 to 40 possible correct answers with the lowest score representing the most severe loss of smell. Anosmia categories were as follows: 0 to 18 = anosmia, 19 to 25 = severe microsmia, 26 to 30 = moderate microsmia, 31 to 34 = mild microsmia, and 35 to 40 = normal.

At baseline, the majority of patients presented with anosmia as demonstrated by median scores of 11.00 and 12.00 for the dupilumab and placebo groups, respectively.

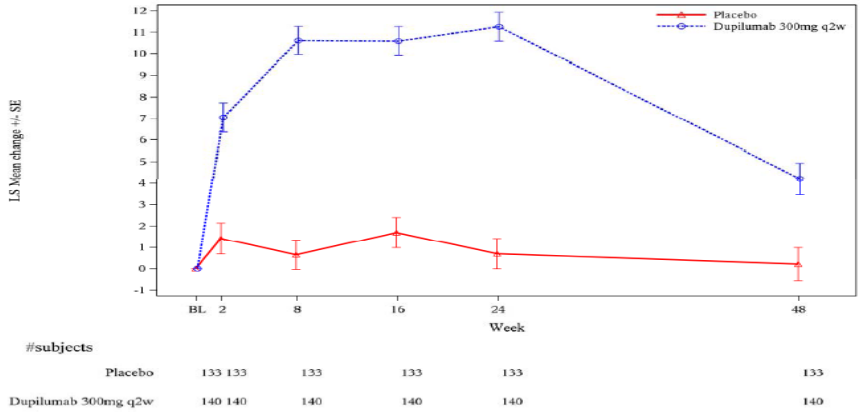
Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab 300 mg q2w displayed a statistically significant improvement in mean UPSIT score compared with placebo at Week 24 (LS mean difference in the dupilumab group versus placebo: 10.56 with 95% CI: 8.79 to 12.34) ($p<0.0001$). The improvement was rapid, noted as early as assessment at Week 2 with an LS mean change from baseline to Week 2 of 7.04 for the dupilumab group and 1.41 for the placebo group (LS mean difference versus placebo: 5.63 with 95% CI: 3.83 to 7.42; $p<0.0001$), and continued through Week 24. At Baseline the vast majority of patients (74.3%) in EFC14146 were anosmic with the UPSIT score of ≤18 at baseline. The proportion of patients with anosmia at Week 24 was reduced from 74.3% at baseline to 23.9% in the dupilumab 300 mg q2w group versus almost no changes in the placebo group (78.2% at baseline and 77.7% at Week 24).

Analysis through the 24-week follow-up period

During the follow up period, UPSIT treatment effect diminished without rebound in the dupilumab group after treatment discontinuation.

LS mean change from baseline in UPSIT score by visit up to Week 48 - ITT population



- **Loss of smell**

The loss of sense of smell severity was reported by the patient on a daily basis using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms).

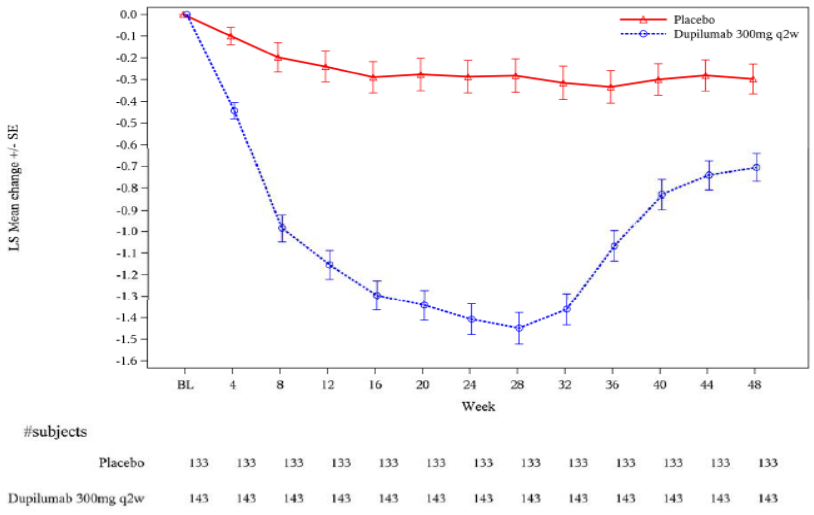
Change from baseline to Week 24 (Multiplicity controlled)

A statistically significant improvement in mean daily assessed sense of smell was seen for the dupilumab group compared with placebo at Week 24 (LS mean difference in the dupilumab group versus placebo: -1.12, 95% CI: -1.31 to -0.93; p<0.0001). The improvement was rapid with an onset of a difference versus placebo observed at Week 4 and showed continued progressive improvement through Week 24.

Analysis through the 24-week follow-up period

After treatment discontinuation the effect on loss of smell diminished without rebound.

LS mean change from baseline in daily assessed loss of smell by month up to Week 48 - ITT population



- 22-Item sino-nasal outcome test (SNOT-22)

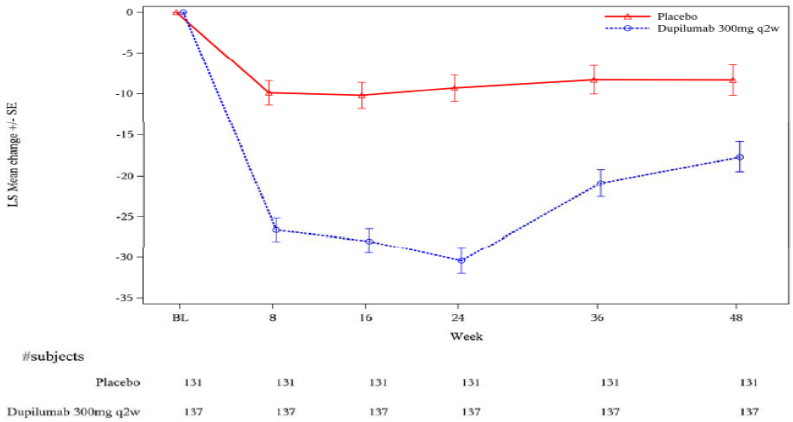
The SNOT-22 has 22 items applicable to sino-nasal conditions and surgical treatments, and each item is scored on a scale from 0 (no problem) to 5 (problem as bad as it can be). The range of the global score was 0 to 110, with higher scores indicating more severe disease.

Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab 300 mg q2w demonstrated a statistically significant improvement in mean SNOT-22 compared with placebo at Week 24 (LS mean difference in the dupilumab group versus placebo: -21.12 with 95% CI: -25.17 to -17.06; p<0.0001). A substantial difference versus placebo in the improvement in SNOT-22 was observed as early as Week 8 with an LS mean change from baseline to Week 8 of -26.62 for the dupilumab group and -9.90 for the placebo group (LS mean difference versus placebo: -16.71 with 95% CI: -20.44 to -12.99; p<0.0001). The SNOT-22 total score showed continued gradual improvement through Week 24.

Analysis through the 24-week follow-up period

During the follow up period, SNOT-22 total score treatment effect diminished without rebound in the dupilumab group after treatment discontinuation.



- **Proportion of patients requiring rescue treatment**

The proportion of patients who required rescue treatment with SCS or NP surgery during the treatment period was lower in the dupilumab group compared to placebo during the 24 week treatment period (Kaplan-Meier estimate of 7.2% versus 23.3%, with a hazard ratio [95% CI] of 0.268 [0.131 to 0.549], nominal p=0.0003).

Proportion of patients with SCS use and/or NP surgery during treatment period – ITT population

	Placebo (N=133)	Dupilumab 300mg q2w (N=143)
Number of patients		
With SCS use/NP surgery	30 (22.6%)	10 (7.0%)
Kaplan-Meier estimates for probability of a patient with >=1 event (95% CI) up to		
16 weeks	0.128 (0.078 to 0.191)	0.049 (0.022 to 0.094)
24 weeks	0.233 (0.164 to 0.310)	0.072 (0.037 to 0.123)
HR, 95% CI vs placebo [a]		0.268 (0.131, 0.549)
P-value vs. placebo [a]		0.0003

a HR: hazard ratio, derived from Cox proportional hazard model with the event of first SCS use and/or NP surgery (actual or planned, whichever is earlier) as the response variable, and treatment, asthma/NSAID-ERD status, prior surgery history and region (pooled countries) as covariates.

Ancillary analyses

Subgroup analyses of the primary endpoints showed generally consistent results across demographic and baseline characteristics (including age, gender, region, territory, race, ethnicity, baseline weight, BMI, prior sino-nasal surgery, asthma and/or NSAID-ERD history).

b) Study EFC14280

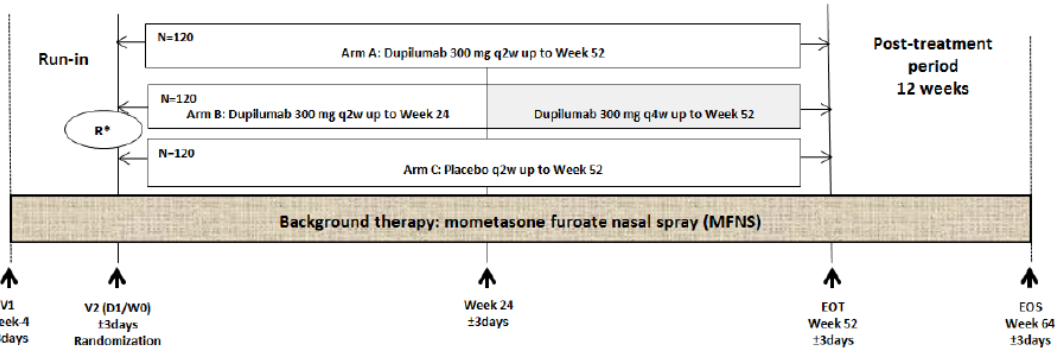
Title

EFC14280: a pivotal Phase 3 study evaluating the effect of dupilumab 300 mg administered subcutaneously q2w for 52 weeks, or q2w for 24 weeks followed by every 4 weeks (q4w) administration to Week 52, in patients with CRSwNP on a background therapy of MFNS.

Methods

Study design

EFC14280 was a multinational, multicenter, randomized, double-blind, Phase 3 placebo-controlled, parallel arm study to evaluate dupilumab in patients with bilateral NP.



R*= Randomization; EOT: end of treatment; EOS: end of study; V: Visit; D: Day; q2w: every 2 weeks; q4w: every 4 weeks;

IMP: Regardless of the treatment group, all randomized patients received q2w subcutaneous administrations of dupilumab or placebo. For Arm B, after Week 24 dupilumab administration was alternated with placebo matched injection every other week up to Week 50 (last IMP administration). Every other week investigational product (IMP) administrations were to be separated by at least 11 days. At V2 the Investigator or delegate was to perform the injection. After V2, every other week administration of IMP was to be performed at the investigational site up to at least Week 8 (V6). Patients were monitored at the study site for at least 30 minutes after injections or minimum time required by local regulator. From Week 10, every other week home administration of IMP (patient, caregiver, or health care professional) was possible if the patient (or the caregiver) was trained. If the patient (or caregiver) was unable or unwilling to administer IMP, arrangements were to be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

Non-investigational medicinal product: mometasone furoate nasal spray (MFNS) was self-administered by the patient twice daily or once daily (if not tolerated twice daily). At each visit the Investigator was to ensure that the patient had the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

The clinical trial consisted of the following 3 periods. In the run-in period (4 weeks) patient's eligibility was determined and the background intranasal corticosteroids were standardised. Patients were to receive MFNS, 2 actuations (50 µg/actuation) in each nostril twice daily (BID; total daily dose of 400 µg). At visit 2 patients were randomized in a 1:1:1 ratio into 3 treatment groups: Group A receiving dupilumab 300 mg q2w SC until Week 52; Group B receiving dupilumab 300 mg q2w SC until Week 24 then switched to dupilumab 300 mg q4w until Week 52 and Group C receiving placebo matching dupilumab SC q2w administration until Week 52. In the randomized treatment period (52 weeks) patients were to continue the stable dose of intranasal MFNS established during the run-in period except if the dose was changed due to an adverse event (AE). Following the EOT at week 52 was the Posttreatment period (12 weeks).

Study participants

A total of 448 patients with CRSwNP were randomized in this study. 295 patients were randomized to dupilumab 300 mg (pool of Arm A+B) with 150 patients randomized to dupilumab 300 mg q2w (Arm A) and 145 patients randomized to dupilumab 300 mg q2w-q4w (Arm B). One hundred and fifty three (153) patients were randomized to placebo. Of the 448 patients randomized, 418 patients completed the first 24 weeks of study treatment. A total of 29 patients discontinued from the study treatment prior to Week 24 (12.4% in placebo versus 3.4% in the dupilumab group) and 1 patient did not receive any study treatment.

- Key inclusion and exclusion criteria for Study EFC14280

Inclusion Criteria	
Diagnostic criteria	Patients with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or who had a medical contraindication/intolerance to SCS; and/or had prior surgery for NP: • An endoscopic bilateral NPS at V1 of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) • Ongoing symptoms (for at least 8 weeks before V1) of: - Nasal congestion/ blockade/obstruction with moderate or severe symptom severity (score 2 or 3) at V1 and a weekly average severity of greater than 1 at time of randomization (V2) AND - Another symptom such as loss of smell, rhinorrhea (anterior/posterior).
Age	≥18 years
Exclusion Criteria	
Prior treatments	Patients who had taken • Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease within 2 months before Visit 1 or 5 half-lives, whichever is longer. • Any experimental monoclonal antibody (mAB) within 5 half-lives or within 6 months before Visit 1 • Anti-IgE therapy (omalizumab) within 130 days prior to Visit 1 • Patients receiving leukotriene antagonists/modifiers at Visit 1 unless on continuous treatment for at least 30 days prior to Visit 1 • Initiation of allergen immunotherapy within 3 months prior to Visit 1
FEV_1	Patients with forced expiratory volume in 1 second (FEV_1) 50% or less of predicted normal were excluded
Prior surgery	Patients who have undergone any intranasal and/or sinus surgery (including polypectomy) within 6 months before screening and patients who had a sino—nasal surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS were excluded
Concomitant conditions/diseases	Antrochoanal polyps, nasal septal deviation that would occlude at least one nostril, acute sinusitis, nasal infection or upper respiratory tract infection, ongoing rhinitis medicamentosa, Allergic granulomatous angiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, concomitant cystic fibrosis, radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis

Treatments

Patients in this study were randomized 1:1:1 into 3 treatment arms:

A. dupilumab 300 mg q2w SC until Week 52

B. dupilumab 300 mg q2w SC until Week 24 then switched to dupilumab 300 mg q4w until Week 52

C. placebo matching dupilumab SC q2w administration until Week 52

Randomization was stratified according to asthma status (history of asthma or not), prior NP surgery (yes or no), and country.

Intranasal corticosteroid background therapy

Mometasone furoate (NASONEX®) 50 micrograms (µg)/actuation nasal spray was provided by the Sponsor in a bottle with 18 g (140 actuations) of product formulation. The patients were to administer 2 actuations (50 µg/actuation) of MFNS in each nostril twice daily (BID) (total daily dose of 400 µg) unless they were intolerant to the BID regimen or this dose was not approved in specific countries, in which case, they were to follow a once daily (QD) regimen.

Rescue treatment

- Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection).
- Short course SCS (prednisone or prednisolone up to 2 weeks).
- Sino-nasal surgery for nasal polyps. Based on previous observations from the POC study, 8 weeks of IMP treatment was recommended prior to surgery to allow onset of treatment effect.

Prohibited concomitant medications

The following concomitant treatments are not permitted during the run-in period and/or the

randomized treatment period:

- Any systemic immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrilomus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide.
- Anti-IgE therapy (omalizumab).
- Allergen immunotherapy (except if initiated more than 3 months prior to V1 and dose stable 1 month prior to V1).
- Intranasal corticosteroid drops.
- Long term courses (>2 weeks) of systemic steroids.
- Short term courses (≤2 weeks) of IV, IM, SC corticosteroids.
- Short course use (≤2 weeks) of OCS between V1 and V2.
- Live, attenuated vaccines (Appendix A).
- Monoclonal antibodies.

Permitted concomitant medications

- MFNS during the run-in period and throughout the whole study.
- Nasal normal saline.
- Single topical decongestants administration for example oxymetazoline hydrochloride (to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic for example lidocaine are allowed before endoscopy.
- Short term use of antibiotics (<2 weeks) are allowed during the study.
- Short-acting β2-adrenoceptor agonist, long-acting β2-adrenoceptor agonist and long-acting muscarinic antagonist.
- Methylxanthines (for example theophylline, aminophyllines).
- Inhaled corticosteroids.
- Systemic antihistamines.
- Leukotriene antagonists/modifiers are permitted during the study, only for patients who were on a continuous treatment for ≥30 days prior to V1.
- Allergen immunotherapy in place for ≥3 months prior to V1 is permitted.

Objectives

The primary objective of this study was to evaluate the efficacy of dupilumab 300 mg every 2 weeks compared to placebo on a background of MFNS in reducing nasal congestion (NC)/obstruction severity and endoscopic nasal polyposis score (NPS) in patients with bilateral nasal polyposis (NP).

The secondary objectives included evaluation of the efficacy of dupilumab in improving total symptoms score (TSS), the efficacy of dupilumab in improving sense of smell, the efficacy of dupilumab in reducing CT scan opacification of the sinuses, the ability of dupilumab to reduce the proportion of patients who require treatment with SCS or surgery for NP, the efficacy of dupilumab on patient reported outcomes (PROs) and healthrelated quality of life (HRQoL) and the effect of dupilumab in the subgroups of patients with prior surgery and comorbid asthma (including NSAID-ERD).

Outcomes/endpoints

There were two co-**primary endpoints**:

- Change from baseline in nasal polyps score at Week 24

  The NPS was assessed by at least 2 physicians based on centrally read video recordings of nasal endoscopy. The score (NPS) was the sum of the right and left nostril scores (range 0 to 8), as evaluated by means of nasal endoscopy. Nasal polyp score was graded based on polyp size in each nostril as described in the Table below. There is no established MCID for NPS. In a study using the same NPS as the current study, a short course of methylprednisolone resulted in a peak difference versus placebo of approximately -2.2 points

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

- Change from baseline in the nasal congestion/obstruction at Week 24

  Nasal congestion/obstruction was scored by the patient as a reflective score, evaluating the symptom severity over the past 24 hours. The NC score was to be recorded by the patient every morning in an e-diary, starting at screening and throughout the study, using the scale presented below.

Scale	Symptoms
0	No symptoms
1	Mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated)
2	Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
3	Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

Secondary endpoints

Key secondary endpoints (hierarchically ordered to account for multiplicity is shown in tab 5):

- Change from baseline in LMK score at week 24
- Change from baseline in TSS at Week 24
- Change from baseline in smell test (UPSIT) at Week 24
- Change from baseline in loss of smell daily symptoms at Week 24
- Change from baseline in SNOT-22 at Week 24
- Change from baseline in LMK score at week 24
  - Proportion of patients requiring rescue treatment defined as: use systemic corticosteroids or NP surgery (actual or planned) during the treatment period

Additional secondary endpoints:

- Change from baseline in NPS at Week 52 for q2w (Arm A) versus placebo (Arm C).
- Change from baseline in NC at Week 52 for q2w (Arm A) versus placebo (Arm C).
- Change from baseline in NPS at Week 52 for q2w/q4w (Arm B) versus placebo (Arm C).
- Change from baseline in NC at Week 52 for q2w/q4w (Arm B) versus placebo (Arm C).

- Comparisons at Week 24 will be made between pooled arms A and B versus placebo.
- Comparisons at Week 52 will be made between Arm A and Arm B versus placebo, separately, and also between Arm A and Arm B.
- Comparisons will be made for the following secondary endpoints:
  - Change from baseline and time course profiles in NC, NPS, TSS, UPSIT, daily assessed loss of smell, SNOT-22 and LMK at Week 52,
  - Change from baseline at Week 24 and Week 52 in: VAS for overall rhinosinusitis, NPIF, and In the severity of rhinorrhea (anterior/posterior nasal discharge) daily symptom score assessed by the patient,
  - Proportion of responders at Week 24 (defined as patients with improvement by at least 1 point in NPS),
  - Proportion of patients with improvement by at least 1 point in NPS and 0.5 reductions in NC at Week 24 and Week 52,
  - Proportion and time-to-event of patients with OCS rescue for any airway exacerbated disease (included but not limited to NP, chronic rhinosinusitis, allergic rhinitis, and asthma),
  - Proportion of patients with minimal clinically important difference (MCID)(≥8.9) in SNOT-22 at Week 24,
  - Proportion of patients with overall rhinosinusitis severity VAS ≤7 at Week 24.

Sample size

The sample size was chosen to enable an adequate characterization of the efficacy between dupilumab 300 mg q2w (pooled A and B arms) and placebo with regard to the 2 co-primary endpoints, changes from baseline in NC and NPS at Week 24.

The observed mean NC reduction of the dupilumab group with qw dosing in ACT12340 is 0.95 and the observed mean NC reduction of the placebo group is 0.26. To calculate power, a conservative estimate was used that assumes the placebo-adjusted NC reduction of the dupilumab 300 mg q2w group is 80% of the dupilumab 300 mg qw group, the mean NC reduction of the dupilumab 300 mg q2w group was then assumed to be 0.81 = 0.8 * (0.95-0.26) + 0.26. Assuming normal distribution of the change in NC, a common standard deviation (SD) of 1.03, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 240 patients for the q2w pool and 120 patients in placebo, the study will have 99% power to detect an effect size of 0.534 using a two-sided test with alpha = 0.05 for the change in NC at Week 24 in the dupilumab 300 mg q2w group.

The observed mean NPS reduction of the dupilumab group with qw dosing in ACT12340 is 1.85 and the observed mean NPS reduction of the placebo group is 0.30. Using same conservative approach that assumes the placebo-adjusted NPS reduction of the dupilumab 300 mg q2w group is 80% of the dupilumab 300 mg qw, the mean NPS reduction of the dupilumab 300 mg q2w group was then assumed to be 1.54 = 0.8*(1.85-0.30)+0.30. Assuming normal distribution of the change in NPS, a common standard deviation (SD) of 2.11, which has incorporated a 20% inflation from the observed SD in ACT12340, and a 25% dropout rate, with 240 patients for the q2w pool and 120 patients in placebo, the study will have 99% power to detect an effect size of 0.588 using a two-sided test with alpha = 0.05 for the change in NPS at Week 24 in the dupilumab 300 mg q2w group. Therefore, with a sample size of 240 patients for the q2w pool (Arm A and B) at Week 24, the combined power of the two co-primary efficacy endpoints is at least 98% for dupilumab 300mg q2w group with alpha = 0.05 assuming no negative correlation between the 2 endpoints.

Randomisation

Approximately 360 patients were to be randomized 1:1:1 into 3 treatment groups as follows:

- Arm A: dupilumab 300 mg q2w SC until Week 52.

- Arm B: dupilumab 300 mg q2w SC until Week 24 then switched to dupilumab 300 mg q4w until Week 52.
- Arm C: placebo matching dupilumab SC q2w administration until Week 52.
-

Randomization was stratified according to asthma status (history of asthma or not), prior NP surgery (yes or no), and country

Blinding (masking)

Dupilumab and placebo were provided in identically matching 2 mL prefilled syringes. To protect the blind, each treatment kit of 2 mL glass prefilled syringes was prepared such that the treatments (dupilumab and its matching placebo) were identical and indistinguishable, and each kit was labeled with a treatment kit number. The randomized treatment kit number list was generated by the Sponsor. Both the patient and Investigator were blinded to assigned active drug or placebo for the entire study period. In addition, to prevent differentiation between the q2w and q4w dosing regimens, after Week 24 dupilumab administration for Arm B was alternated with a placebo matched injection every other week. Study patients, Investigators, and study site personnel did not have access to the randomization codes unless immediate unblinding was necessary to protect patient safety in an emergency.

Statistical methods

The primary analysis population for the efficacy endpoints will be the randomized ITT population which includes all patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they were randomized.

Primary statistical model (ITT analysis)

Each of the 2 co-primary efficacy endpoints (3 co-primary efficacy endpoints for Japan) will be analysed using a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. Data collected after treatment discontinuation will be included in the analysis. With this approach, for patients who undergo surgery for NP or receive SCS for any reason, data collected postsurgery (actual date) or post SCS will be set to missing, and the worst post-baseline value on or before the time of surgery or SCS will be used to impute missing Week 24 value (for patients whose postbaseline values are all missing, the baseline will be used to impute). For patients who discontinue the treatment without being rescued by surgery or receiving SCS, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all patients who have not been rescued by surgery or receiving SCS at Week 24. Each of the imputed complete data will be analysed by fitting an ANCOVA model with the baseline value of the corresponding co-primary endpoint, treatment group, asthma/NERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

Sensitivity analyses

For all sensitivity analyses, except for the as-observed analysis, for patients who underwent surgery for NP or received SCS for any reason, data collected post-surgery or post SCS were be set to missing. The sensitivity analyses are summarized below.

- Mixed-effect model with repeated measures (MMRM) approach: The model included change from baseline values up to Week 24 as response variables, and factors (fixed effects) for treatment, stratification factor, visit, treatment-by-visit interaction, NPS/NC baseline value and baseline-by-visit interaction. Data collected after

treatment discontinuation was included in the analysis. No imputation was performed for the MMRM model.

- Pattern mixture model with copy increment from placebo: Each of the co-primary efficacy endpoints was analysed with imputed missing values at Week 24 using pattern mixture model with copy increment from placebo (34). This copy increment from placebo implied that when patients discontinued treatment early, they continued to take advantage of their previous therapy, but they progressed in the same way as patients in the placebo group. The imputed dataset was analysed by fitting an ANCOVA model as for the primary analysis.
- Tipping point analysis: Each of the co-primary efficacy endpoints was subject to a tipping point analysis with imputed missing value at Week 24.
- As-observed analysis: An additional analysis was conducted on the co-primary efficacy endpoints which included all data (including that collected after SCS for any reason and/or treatment discontinuation) but excluded post NP surgery data. The data were analysed in the same ANCOVA model for the primary approach.
- Mixed-effect model with repeated measures (MMRM) approach for NC as binary response data: In the primary analysis, NC was analyzed as the average of 28-day NC data. To assess the robustness of this approach, an MMRM approach on NC as longitudinal binary response data was performed based on methods proposed and evaluated by Fan (35).

Multiplicity issues

A hierarchical testing procedure was prespecified to control the overall type-I error rate for testing the co-primary and selected secondary endpoints. The overall alpha was 0.05. The comparisons with placebo were tested based on the hierarchical order in Table 5 at 2-sided $\alpha = 0.05$.

Table 5 – Hierarchical testing order for co-primary and selected secondary endpoints

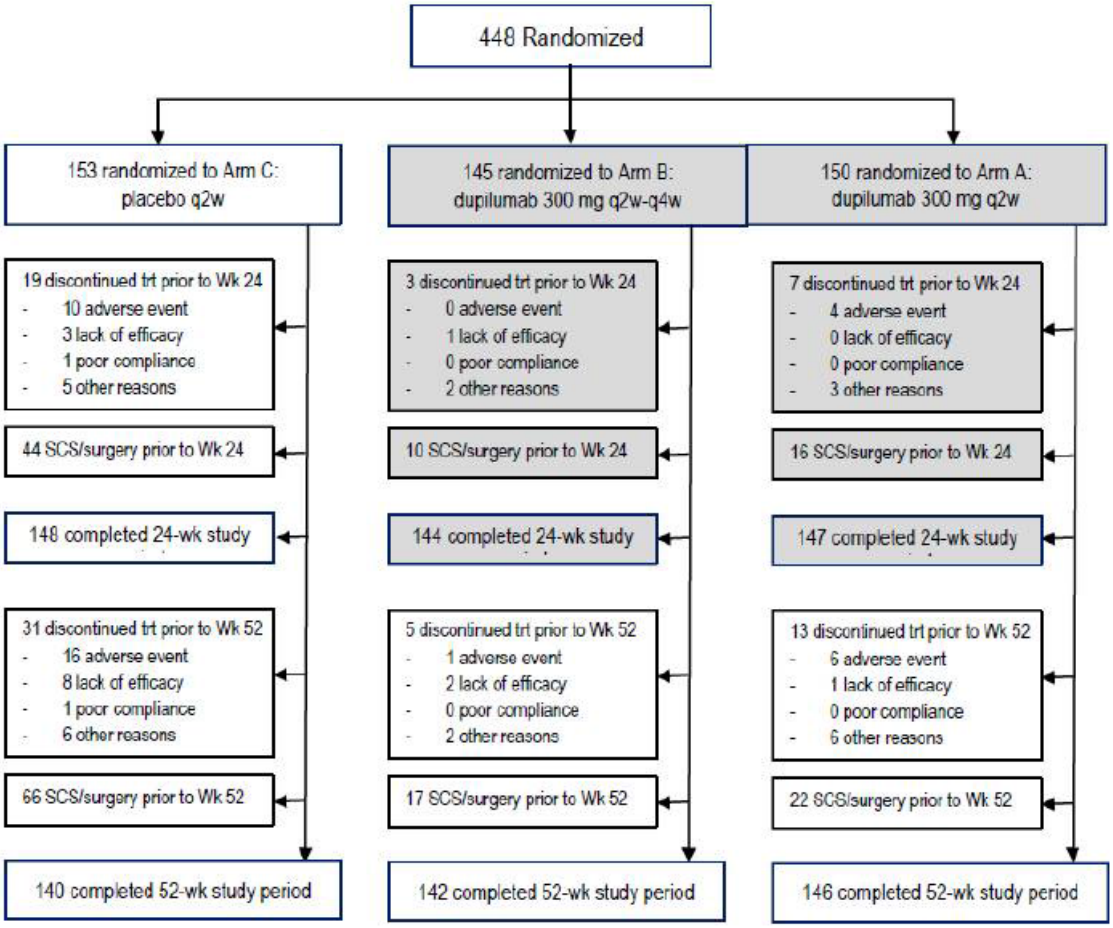
	Endpoints	Comparison
Coprimary	Change from baseline in bilateral NPS at Week 24	Dupilumab 300 mg q2w (Arm A+B) vs placebo
	Change from baseline in NC at Week 24	
Key secondary[a]	Change from baseline in LMK score at Week 24[b]	Dupilumab 300 mg q2w (Arm A+B) vs placebo
	Change from baseline in TSS at Week 24	
	Change from baseline in smell test (UPSIT) at Week 24	
	Change from baseline in loss of smell daily symptoms at Week 24	
	Change from baseline in SNOT-22 at Week 24	
	Change from baseline in NPS at Week 52	Dupilumab 300 mg q2w (Arm A) vs placebo
	Change from baseline in NC at Week 52	
	Change from baseline in SNOT-22 at Week 52	

a In addition to the key secondary endpoints listed, 2 pre-specified analyses based on pooled data from Study EFC14280 and EFC14146 were included in the hierarchy: Proportion of patients requiring rescue with SCS or NP surgery and FEV_1 at Week 24. The results of the pooled analyses are provided in 2.7.3 Summary of Clinical Efficacy.

b Change from baseline in LMK score is a coprimary endpoint in Japan.

Results

Participant flow



806 patients signed the written informed consent and were screened for study eligibility. 448 patients were enrolled, for a screen failure rate of 44.4%. The leading reasons for screen failure were failure to meet the inclusion criterion of a minimum score of 5 points on the bilateral NPS, failure to meet the inclusion criteria for ongoing symptoms with an NC score of 2 or 3 and another symptom and noncompliance with the NIMP at Visit 2.

A total of 150 patients were randomized to Arm A and 145 patients were randomized to Arm B. 153 patients were randomized to Arm C for 52 weeks. One patient was randomized to the placebo group but did not receive treatment. Study treatment discontinuation prior to Week 24 occurred at a lower rate in the dupilumab group compared with the placebo group (10 [3.4%] patients and 19 [12.4%] patients in the dupilumab 300 mg q2w and placebo groups, respectively). 398 patients completed 52 weeks of treatment with the study medication. Treatment discontinuation rates were lower in the dupilumab groups compared with the placebo group (8.7% and 3.4% patients in the dupilumab 300 mg q2w and 300 mg q2wq4w groups, respectively, and 20.3% patients in the placebo group). 15 patients had a surgery during the study treatment (2 patients in the dupilumab 300 mg q2w group, 1 patient in the 300 mg q2w-q4w group, and 12 patients in the placebo group).

The description above is based on the data from the initially submitted CSR and is unchanged as the treatment period of all non-discontinued patients was completed at the time of the initial data cut-off date. At that time, 428 patients had completed the 52-week treatment period with or without study medication, with 159 patients having completed the whole study period, and 260 patients still in the post-treatment follow-up period. All patients have since completed the study.

The updated patient disposition as of the end of the study is provided below.

	Placebo (N=153)	Dupilumab 300mg q2w-q4w (N=145)	Dupilumab 300mg q2w (N=150)
Randomized and not treated	1 (0.7%)	0	0
Not treated per patient's request	0	0	0
Randomized and treated	152 (99.3%)	145 (100%)	150 (100%)
Completed study treatment during the randomized treatment period	121 (79.1%)	140 (96.6%)	137 (91.3%)
Completed the first 24-week study treatment period	133 (86.9%)	142 (97.9%)	143 (95.3%)
Discontinued study treatment during the first 24-week study treatment period	19 (12.4%)	3 (2.1%)	7 (4.7%)
Discontinued study treatment during the randomized treatment period	31 (20.3%)	5 (3.4%)	13 (8.7%)
Study treatment discontinuation prior to Week 24 per patient's request	15 (9.8%)	3 (2.1%)	4 (2.7%)
Reason for study treatment discontinuation prior to Week 24			
Adverse event	10 (6.5%)	0	4 (2.7%)
Lack of efficacy	3 (2.0%)	1 (0.7%)	0
Poor compliance to protocol	1 (0.7%)	0	0
Other reason	5 (3.3%)	2 (1.4%)	3 (2.0%)
Patients with first SCS/surgery prior to Week 24 (study day 169)	44 (28.8%)	10 (6.9%)	16 (10.7%)
Study treatment discontinuation prior to Week 52 per patient's request	22 (14.4%)	5 (3.4%)	7 (4.7%)
Reason for study treatment discontinuation prior to Week 52			
Adverse event	16 (10.5%)	1 (0.7%)	6 (4.0%)
Lack of efficacy	8 (5.2%)	2 (1.4%)	1 (0.7%)
Poor compliance to protocol	1 (0.7%)	0	0
Other reason	6 (3.9%)	2 (1.4%)	6 (4.0%)
Patients with first SCS/surgery prior to Week 52 (study day 365)	67 (43.8%)	17 (11.7%)	22 (14.7%)
Completed the 24-week study period	148 (96.7%)	144 (99.3%)	147 (98.0%)
Completed the 52-week study period	139 (90.8%)	142 (97.9%)	146 (97.3%)
Discontinued from the study prior to Week 24	5 (3.3%)	1 (0.7%)	3 (2.0%)
Discontinued from the study prior to Week 52	14 (9.2%)	3 (2.1%)	4 (2.7%)
Reason for study discontinuation prior to Week 24			
Adverse event	1 (0.7%)	0	2 (1.3%)
Poor compliance to protocol	0	0	0
Study terminated by sponsor	0	0	0
Other reason	4 (2.6%)	1 (0.7%)	1 (0.7%)
Reason for study discontinuation prior to Week 52			
Adverse event	1 (0.7%)	0	2 (1.3%)
Poor compliance to protocol	1 (0.7%)	0	0
Study terminated by sponsor	0	0	0
Other reason	11 (7.2%)	3 (2.1%)	2 (1.3%)

Ongoing in study	0	0	0
Completed the study period	136 (88.9%)	140 (96.6%)	144 (96.0%)
Discontinued from the study period	17 (11.1%)	5 (3.4%)	6 (4.0%)
Reason for study discontinuation			
Adverse event	4 (2.6%)	1 (0.7%)	2 (1.3%)
Poor compliance to protocol	1 (0.7%)	0	0
Study terminated by sponsor	0	0	0
Other reason	12 (7.8%)	4 (2.8%)	4 (2.7%)
Status at last study contact			
Dead	0	1 (0.7%)	0

Note: percentages are calculated using the number of patients randomized as denominator
PGM=PRODOPS/SAR231893/EFC14280/CSR_2/REPORT/PGM/dis_dispo_r_t.sas OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (01FEB2019 - 4:12)

Recruitment

The cut-off for data included in the CSR was the date when the last patient completed the last treatment visit (29 August 2018). At the time of this data cut-off, some patients were still in the posttreatment period. The data collected after the cut-off date were submitted in an addendum with the responses to the 1st RSI.

Conduct of the study

- Amendments

One global amendment was made to the study protocol:

No.	Date	Purpose of amendments
1	17 May 2017	• Reworded for clarity the procedures to be performed at permanent treatment discontinuation. In addition, added the assessment of rhinorrhea anterior and posterior following early treatment discontinuation to support total symptom score analysis. • Permitted 1 retest of dynamic laboratory tests (ie, those subject to variability) during screening at the discretion of the Investigator • Clarified that the analysis of the proportion of patients who used systemic corticosteroids (SCS) was to include all SCSs (not just oral corticosteroid) • Elevated European quality of life 5D scale (EQ-5D) from exploratory endpoint to secondary efficacy endpoint • Clarified that CT scan was mandatory unless not approved by local ethics committee or IRB • Intranasal decongestants added to list of prohibited medications except as needed for nasal endoscopy procedure • Permitted study procedures to be performed over 3 days, if necessary, as long as within the visit window • Deleted the requirement for male birth control (to be consistent with most current safety information) • Correction of typographical and other minor changes

- Protocol deviations

38.7% of patients in the dupilumab 300 mg q2w group, 40.7% of patients in the 300 mg q2w-q4w group, and 49.7% of patients in the placebo group had a deviation. The most frequently occurring included deviations in the schedule of assessments or procedures (eg, a study visit or phone call not performed or performed outside of the visit window) occurring in 15.9% to 24.8% of patients and deviations in IMP management (eg, missed IMP dose, or IMP administered but not per protocol) occurring in 15.3% to 21.6% of patients.

Critical or major deviations that could potentially impact efficacy analyses were identified by the applicant. These included failure to meet the inclusion criteria or violation of exclusion criteria related to the co-primary efficacy endpoints, use of prohibited concomitant medications that interfere with the primary analysis approach on SCS rescue, missing co-primary efficacy endpoint assessments, or noncompliance or randomization procedures that result in <80% compliance with

the IMP). The numbers reported were small with 5 (3.3%) in the 300 mg q2w group and 6 (4.1%) patients in the 300 mg q2w-q4w group and 9 (5.9%) patients in the placebo group.

Similar protocol amendments and changes in the planned analyses were made in both studies. These changes were unlikely to have a significant impact on the study results. In both studies a number of patients had a deviation considered critical or major (Study EFC14146: 29.4% of patients in the dupilumab group and 42.9% of patients in the placebo group, Study EFC14280: 38.7% of patients in the dupilumab 300 mg q2w group, 40.7% of patients in the 300 mg q2w-q4w group, and 49.7% of patients in the placebo group).

Baseline data

Patients enrolled in this study had severe CRSwNP disease as reflected by baseline mean NPS of 6.10 (maximum of 8), mean NC symptom score of 2.43 (maximum of 3), mean SNOT-22 total score of 51.86 (maximum possible score 110), mean UPSIT score of 13.61 (indicating anosmia score of 0 to 18, maximum score of 40]) and mean TSS of 7.22 (maximum of 9). The mean AS for rhinosinusitis was 8.0 (severe disease >7) and mean loss of smell at baseline was 2.75 (maximum score of 3). Upon CT-scan evaluation, most patients had extensive opacification of the sinuses bilaterally as assessed by the LMK total mean score of 17.96 (maximum of 24). The majority of patients (90%) had at least partial opacification of all sinuses. The mean blood eosinophil count at baseline was high (0.43 Giga/L). The mean time since first diagnosis of CRSwNP was 10.94 years and ranged from 0.1 to 61.3 years. The mean age of onset was 41.06 years.

Demographics and patient characteristics at baseline - Randomized population

	Placebo (N=153)	Dupilumab 300mg q2w-q4w (N=145)	Dupilumab 300mg q2w (N=150)	All (N=448)
Age (years)				
Number	153	145	150	448
Mean (SD)	51.67 (12.66)	52.28 (12.87)	51.91 (11.88)	51.95 (12.45)
Median	53.00	53.00	51.00	52.00
Q1 : Q3	44.00 : 61.00	42.00 : 63.00	42.00 : 61.00	43.00 : 62.00
Min : Max	22.0 : 80.0	20.0 : 83.0	18.0 : 81.0	18.0 : 83.0
Age group (years) [n (%)]				
Number	153	145	150	448
18 - 64	129 (84.3%)	113 (77.9%)	125 (83.3%)	367 (81.9%)
65 - 74	22 (14.4%)	27 (18.6%)	23 (15.3%)	72 (16.1%)
75 - 84	2 (1.3%)	5 (3.4%)	2 (1.3%)	9 (2.0%)
≥ 85	0	0	0	0
Sex [n (%)]				
Number	153	145	150	448
Male	95 (62.1%)	87 (60.0%)	97 (64.7%)	279 (62.3%)
Female	58 (37.9%)	58 (40.0%)	53 (35.3%)	169 (37.7%)
Region[a] [n (%)]				
Number	153	145	150	448
Asia	16 (10.5%)	17 (11.7%)	16 (10.7%)	49 (10.9%)
Latin America	44 (28.8%)	44 (30.3%)	49 (32.7%)	137 (30.6%)
East Europe	16 (10.5%)	13 (9.0%)	14 (9.3%)	43 (9.6%)
Western Countries	77 (50.3%)	71 (49.0%)	71 (47.3%)	219 (48.9%)
Territory[b] [n (%)]				
Number	153	145	150	448
North America	29 (19.0%)	30 (20.7%)	30 (20.0%)	89 (19.9%)
European Union	30 (19.6%)	29 (20.0%)	28 (18.7%)	87 (19.4%)
Rest of World	94 (61.4%)	86 (59.3%)	92 (61.3%)	272 (60.7%)
Race [n (%)]				
Number	153	145	150	448
Caucasian/White	128 (83.7%)	120 (82.8%)	124 (82.7%)	372 (83.0%)
Black/of African descent	3 (2.0%)	2 (1.4%)	2 (1.3%)	7 (1.6%)
Asian/Oriental	18 (11.8%)	19 (13.1%)	17 (11.3%)	54 (12.1%)
Japanese	17 (11.1%)	17 (11.7%)	16 (10.7%)	50 (11.2%)
American Indian or Alaska Native	3 (2.0%)	2 (1.4%)	7 (4.7%)	12 (2.7%)
Native Hawaiian or Other Pacific Islander	0	1 (0.7%)	0	1 (0.2%)
Multiple	1 (0.7%)	1 (0.7%)	0	2 (0.4%)
Unknown	0	0	0	0
Ethnicity [n (%)]				
Number	153	144	150	447
Hispanic or Latino	40 (26.1%)	42 (29.2%)	50 (33.3%)	132 (29.5%)
Not Hispanic or Latino	113 (73.9%)	102 (70.8%)	100 (66.7%)	315 (70.5%)
Weight (kg)				
Number	153	145	150	448
Mean (SD)	80.26 (17.84)	79.47 (17.59)	79.89 (18.24)	79.88 (17.86)
Median	79.00	78.00	79.00	79.00
Q1 : Q3	67.50 : 91.00	67.00 : 91.00	68.20 : 89.50	67.15 : 90.75
Min : Max	45.0 : 139.7	39.4 : 137.3	43.1 : 149.5	39.4 : 149.5

Weight group (kg) [n (%)]				
Number	153	145	150	448
< 70	47 (30.7%)	45 (31.0%)	43 (28.7%)	135 (30.1%)
≥ 70 - < 90	61 (39.9%)	58 (40.0%)	70 (46.7%)	189 (42.2%)
≥ 90	45 (29.4%)	42 (29.0%)	37 (24.7%)	124 (27.7%)
Body mass index (BMI) (kg/m^2)				
Number	153	145	150	448
Mean (SD)	27.91 (5.50)	27.96 (5.51)	27.96 (5.53)	27.94 (5.50)
Median	27.48	27.44	27.06	27.38
Q1 : Q3	23.88 : 31.25	24.22 : 30.82	24.39 : 30.80	24.20 : 30.91
Min : Max	17.5 : 45.8	16.4 : 52.3	18.0 : 59.9	16.4 : 59.9
Smoking history [n(%)]				
Number	153	145	150	448
Former	49 (32.0%)	43 (29.7%)	40 (26.7%)	132 (29.5%)
Current	17 (11.1%)	11 (7.6%)	14 (9.3%)	42 (9.4%)
Never	87 (56.9%)	91 (62.8%)	96 (64.0%)	274 (61.2%)
Cessation prior to screening (months)				
Number	49	43	40	132
Mean (SD)	215.45 (161.99)	213.26 (168.48)	214.00 (155.47)	214.30 (160.97)
Median	175.00	183.00	195.00	184.00
Q1 : Q3	67.00 : 366.00	67.00 : 306.00	109.00 : 262.50	80.50 : 310.00
Min : Max	1.0 : 533.0	6.0 : 691.0	5.0 : 691.0	1.0 : 691.0
Pack-year				
Number	55	46	42	143
Mean (SD)	15.97 (25.33)	13.81 (22.54)	11.90 (15.05)	14.08 (21.75)
Median	6.30	5.50	7.00	6.30
Q1 : Q3	1.00 : 20.00	1.00 : 13.50	1.25 : 17.00	1.10 : 17.00
Min : Max	0.0 : 117.0	0.1 : 120.0	0.1 : 70.0	0.0 : 120.0

80.1% of the patients received at least one course of SCS in the 2 years prior to randomization. 96.9% of patients had either SCS in past two years or prior surgery for nasal polyp. 59.6% of patients had a history of asthma and 26.8% had a history of NSAID-ERD. 82.4% had a medical history of at least 1 comorbid type 2 inflammatory disease. The incidence of patients with each type 2 inflammatory condition was similar among treatment groups.

Summary of history of prior NP surgery, systemic corticosteroid use, and epistaxis - Randomized population

	Placebo (N=153)	Dupilumab 300mg q2w-q4w (N=145)	Dupilumab 300mg q2w (N=150)	All (N=448)
Time since first diagnosis of nasal polyposis (years)				
Number	151	144	148	443
Mean (SD)	10.88 (9.40)	10.67 (9.12)	11.28 (10.38)	10.94 (9.63)
Median	7.52	7.71	9.05	8.21
Q1 : Q3	3.67 : 16.64	4.45 : 15.70	3.49 : 16.81	3.90 : 16.27
Min : Max	0.2 : 42.3	0.2 : 55.1	0.1 : 61.3	0.1 : 61.3
Age of onset of nasal polyposis (years)				
Number	151	144	148	443
Mean (SD)	40.97 (14.54)	41.65 (13.87)	40.59 (13.39)	41.06 (13.92)
Median	42.00	41.00	41.50	41.00
Q1 : Q3	29.00 : 53.00	32.00 : 52.00	30.00 : 50.50	30.00 : 51.00
Min : Max	10.0 : 75.0	7.0 : 76.0	9.0 : 70.0	7.0 : 76.0
Number of patients with prior surgery from IVRS	91 (59.5%)	86 (59.3%)	89 (59.3%)	266 (59.4%)
Number of patients with prior surgery for nasal polyposis and/or SCS use during the past 2 years	148 (96.7%)	140 (96.6%)	146 (97.3%)	434 (96.9%)
Number of patients with prior surgery for nasal polyposis	88 (57.5%)	85 (58.6%)	88 (58.7%)	261 (58.3%)
Number of previous surgeries for nasal polyposis				
Number[a]	88 (57.5%)	85 (58.6%)	88 (58.7%)	261 (58.3%)
Mean (SD)	1.76 (1.37)	1.54 (1.17)	1.93 (1.57)	1.75 (1.39)
Median	1.00	1.00	1.00	1.00
Q1 : Q3	1.00 : 2.00	1.00 : 2.00	1.00 : 2.50	1.00 : 2.00
Min : Max	1.0 : 8.0	1.0 : 8.0	1.0 : 11.0	1.0 : 11.0
1	56 (63.6%)	59 (69.4%)	49 (55.7%)	164 (62.8%)
2	14 (15.9%)	17 (20.0%)	17 (19.3%)	48 (18.4%)
≥3	18 (20.5%)	9 (10.6%)	22 (25.0%)	49 (18.8%)
Time since most recent nasal polyposis surgery (years)				
Number	88	84	88	260
Mean (SD)	8.77 (7.15)	8.41 (6.83)	7.54 (7.02)	8.24 (7.00)
Median	7.56	6.58	5.54	6.58
Q1 : Q3	3.60 : 11.67	3.43 : 11.03	2.56 : 9.64	3.31 : 10.64
Min : Max	0.6 : 37.4	0.7 : 36.5	0.6 : 41.6	0.6 : 41.6

Number of patients with SCS use during the past 2 years	122 (79.7%)	116 (80.0%)	121 (80.7%)	359 (80.1%)
Number of courses[b] with SCS use during the past 2 years				
Number[c]	122 (79.7%)	116 (80.0%)	121 (80.7%)	359 (80.1%)
Mean (SD)	1.49 (0.95)	1.72 (1.60)	1.61 (1.37)	1.60 (1.33)
Median	1.00	1.00	1.00	1.00
Q1 : Q3	1.00 : 2.00	1.00 : 2.00	1.00 : 2.00	1.00 : 2.00
Min : Max	1.0 : 7.0	1.0 : 12.0	1.0 : 11.0	1.0 : 12.0
1	86 (70.5%)	77 (66.4%)	85 (70.2%)	248 (69.1%)
2	21 (17.2%)	24 (20.7%)	21 (17.4%)	66 (18.4%)
3	9 (7.4%)	7 (6.0%)	6 (5.0%)	22 (6.1%)
4	5 (4.1%)	1 (0.9%)	3 (2.5%)	9 (2.5%)
≥5	1 (0.8%)	7 (6.0%)	6 (5.0%)	14 (3.9%)
Number of days with SCS use during the past 2 years				
Number[d]	75 (49.0%)	55 (37.9%)	67 (44.7%)	197 (44.0%)
Mean (SD)	18.52 (39.62)	59.35 (146.18)	64.22 (149.00)	45.46 (120.03)
Median	10.00	14.00	12.00	11.00
Q1 : Q3	6.00 : 20.00	8.00 : 31.00	8.00 : 22.00	7.00 : 24.00
Min : Max	1.0 : 341.0	1.0 : 732.0	1.0 : 704.0	1.0 : 732.0
Number[e]	122 (79.7%)	116 (80.0%)	121 (80.7%)	359 (80.1%)
>0-≤7	28/122 (23.0%)	11/116 (9.5%)	14/121 (11.6%)	53/359 (14.8%)
>7-≤14	23/122 (18.9%)	18/116 (15.5%)	25/121 (20.7%)	66/359 (18.4%)
>14-≤21	8/122 (6.6%)	4/116 (3.4%)	11/121 (9.1%)	23/359 (6.4%)
>21-≤28	2/122 (1.6%)	4/116 (3.4%)	2/121 (1.7%)	8/359 (2.2%)
>28-≤56	13/122 (10.7%)	11/116 (9.5%)	6/121 (5.0%)	30/359 (8.4%)
>56-≤84	0/122	0/116	0/121	0/359
>84-≤112	0/122	1/116 (0.9%)	0/121	1/359 (0.3%)
>112	7/122 (5.7%)	13/116 (11.2%)	17/121 (14.0%)	37/359 (10.3%)
Undetermined duration	41/122 (33.6%)	54/116 (46.6%)	46/121 (38.0%)	141/359 (39.3%)

Numbers analysed

448 patients (150 patients in the dupilumab 300 mg q2w group, 145 patients in the dupilumab 300 mg q2w-q4w group, and 153 patients in the placebo group) were randomized and included in the ITT group, which was the primary population for the efficacy analyses in this study.

Analysis population - Randomized population

	Placebo (N=153)	Dupilumab 300mg q2w-q4w (N=145)	Dupilumab 300mg q2w (N=150)	All (N=448)
Randomized population	153 (100%)	145 (100%)	150 (100%)	448 (100%)
Efficacy population				
Intent-to-Treat (ITT)	153 (100%)	145 (100%)	150 (100%)	448 (100%)
Safety population	150	148	149	447
PK population	0	146	149	295
ADA population	149	148	148	445

Note: For the safety, PK and ADA population, patients are tabulated according to treatment actually received (as treated)

Outcomes and estimation

Summary of the primary and selected secondary endpoint in the hierarchical testing procedure

	Placebo (N=153)			Dupilumab 300mg q2w (N=295)				
	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Absolute Difference for Dupilumab vs. Placebo LS Mean (95% CI)	P Value
Primary endpoints								
Bilateral nasal polyps score (NPS) at Week 24	5.96 (1.21)	6.09 (1.19)	0.10 (0.14)	6.18 (1.21)	4.46 (1.89)	-1.71 (0.11)	-1.80 (-2.10, -1.51)	<.0001
Nasal congestion/obstruction (NC) at Week 24	2.38 (0.54)	2.02 (0.77)	-0.38 (0.07)	2.46 (0.61)	1.19 (0.90)	-1.25 (0.06)	-0.87 (-1.03, -0.71)	<.0001
Key secondary endpoints								
Lund Mackay score (LMK) at Week 24	17.65 (3.76)	17.73 (3.81)	-0.09 (0.31)	18.12 (3.75)	12.86 (3.87)	-5.21 (0.24)	-5.13 (-5.80, -4.46)	<.0001
Total symptom score (TSS) at Week 24	7.08 (1.38)	6.08 (1.97)	-1.00 (0.20)	7.30 (1.48)	3.77 (2.44)	-3.45 (0.15)	-2.44 (-2.87, -2.02)	<.0001
Smell test (UPSIT) at Week 24	13.78 (8.31)	13.30 (7.96)	-0.81 (0.71)	13.53 (7.88)	23.89 (9.21)	9.71 (0.56)	10.52 (8.98, 12.07)	<.0001
Loss of smell at Week 24	2.72 (0.52)	2.49 (0.79)	-0.23 (0.08)	2.77 (0.53)	1.55 (1.02)	-1.21 (0.06)	-0.98 (-1.15, -0.81)	<.0001
SNOT-22 at Week 24	53.48 (21.85)	42.16 (23.26)	-10.40 (1.61)	51.02 (20.37)	23.89 (18.77)	-27.77 (1.26)	-17.36 (-20.87, -13.85)	<.0001
Bilateral nasal polyps score (NPS) at Week 52	5.96 (1.21)	6.10 (1.52)	0.15 (0.15)	6.07 (1.22)	3.76 (2.20)	-2.24 (0.15)	-2.40 (-2.77, -2.02)	<.0001
Nasal congestion/obstruction (NC) at Week 52	2.38 (0.54)	2.04 (0.78)	-0.37 (0.08)	2.48 (0.62)	1.10 (0.92)	-1.35 (0.07)	-0.98 (-1.17, -0.79)	<.0001
SNOT-22 at Week 52	53.48 (21.85)	44.05 (22.66)	-8.88 (1.61)	50.16 (19.72)	21.67 (19.16)	-29.84 (1.63)	-20.96 (-25.03, -16.89)	<.0001

Dupilumab 300 mg q2w: pooled Arm A and B for comparisons at Week 24, and Arm A only for comparisons at Week 52. Arm A: 300mg q2w. Arm B: 300 mg q2w-q4w.
PGM=PRODOPS/SAR231893/EFC14280/CSR/REPORT/PGM/eff_hierarchical_test_i_t.sas OUT=REPORT/OUTPUT/eff_hierarchical_test_i_t_i.rtf (02DEC2018 - 14:08)

Note: The ranges of possible scores for each endpoint were as follows, with the highest score representing most severe disease: NPS (0 to 8), NC score (0 to 3), LMK (0 to 24), TSS (0 to 9), loss of smell (0 to 3), SNOT-22 total score (0 to 110, with an MCID of 8.9). The range for the UPSIT was 0 to 40 (with lowest score representing most severe loss of smell and scores ≤18 classified as anosmia).

Of note, in the following sections the results from endpoints related to the same efficacy score are described together for the convenience of reading.

CO-PRIMARY ENDPOINTS

- **CHANGE FROM BASELINE IN NASAL POLYPOSIS SCORE (NPS)**

Primary analysis: Change from baseline in nasal polyps score at Week 24

The results show a statistically significant improvement in the mean bilateral endoscopic NPS compared with placebo at Week 24, with an LS mean change from baseline to Week 24 of -1.71 for the 300 mg q2w dupilumab group (pooled Arm A+B) and +0.10 for the placebo group (LS mean difference versus placebo: -1.80 with 95% CI: -2.10 to -1.51; p<0.0001). The onset of

improvement was seen at week4 with an LS mean change from baseline to Week 4 of -1.11 for the 300 mg q2w dupilumab group [pooled Arm A+B] and +0.05 for the placebo group (LS mean difference versus placebo: -1.15 with 95% CI: -1.40 to -0.91; nominal p<0.0001). The NPS showed progressive improvement through Week 24.

Primary approach: change from baseline in bilateral nasal polyps score (NPS) at Week 24 - ITT population

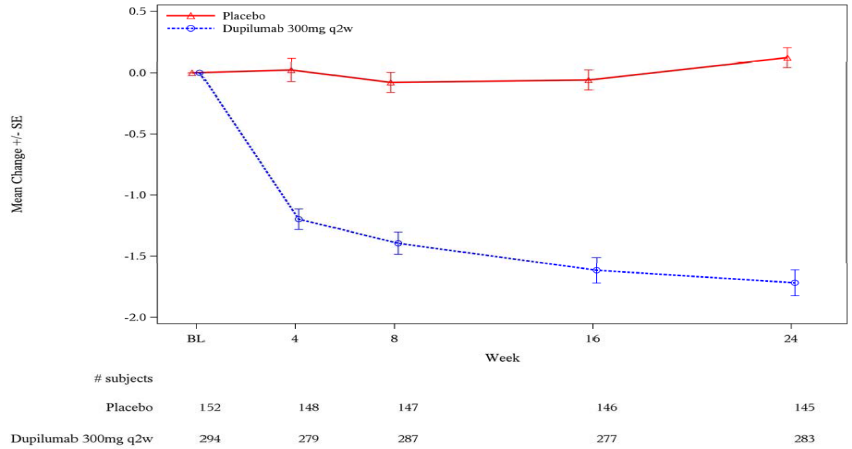
NPS	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	152	294
Mean (SD)	5.96 (1.21)	6.18 (1.21)
Median	6.00	6.00
Q1 : Q3	5.50 : 7.00	5.50 : 7.00
Min : Max	2.0 : 8.0	1.5 : 8.0
Week 24		
Number	145	283
Mean (SD)	6.09 (1.19)	4.46 (1.89)
Median	6.00	4.50
Q1 : Q3	5.50 : 7.00	3.50 : 6.00
Min : Max	3.5 : 8.0	0.0 : 8.0
Change from baseline		
Number	145	283
Mean (SD)	0.12 (0.95)	-1.72 (1.77)
Median	0.00	-1.50
Q1 : Q3	-0.50 : 0.50	-3.00 : -0.50
Min : Max	-2.0 : 3.5	-6.0 : 4.5
LS Mean (SE) [a]	0.10 (0.14)	-1.71 (0.11)
LS Mean Diff vs. placebo (95% CI) [a]		-1.80 (-2.10, -1.51)
P-value vs. placebo [a]		<.0001

Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Sensitivity analyses

The results of the sensitivity analyses (MMRM, RMM, As-observed analysis) demonstrated similar results to those of the primary WOCF/MI analysis.

LS mean change from baseline in bilateral nasal polyps score (NPS) by visit up to Week 24 - ITT population



Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.

Key secondary efficacy endpoint: Change from baseline at Week 52 (Multiplicity controlled)

Dupilumab 300 mg q2w demonstrated a statistically significant improvement in the mean bilateral endoscopic NPS compared with placebo at Week 52 (LS mean difference in the 300 mg q2w

dupilumab [Arm A] group versus placebo: -2.40 with 95% CI: -2.77 to -2.02; p<0.0001). The LS mean difference in the 300 mg q2w dupilumab group versus placebo at Week 52 was greater than that observed at Week 24, indicating a continued improvement through 52 weeks.

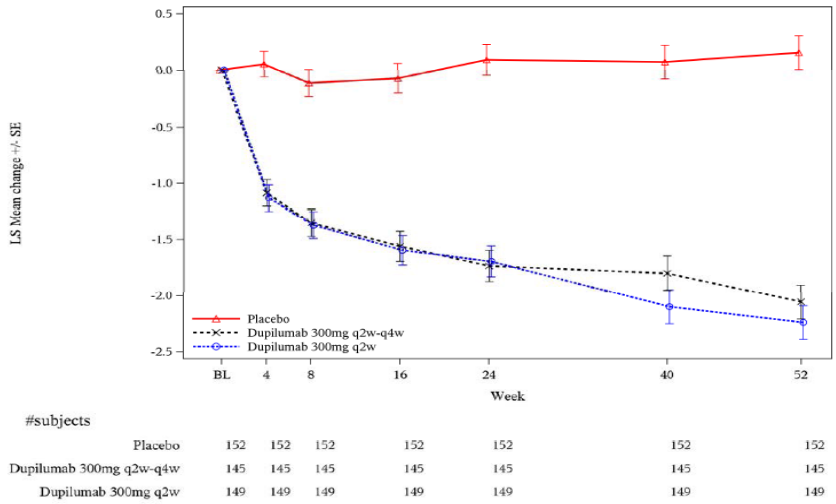
Change from baseline in bilateral nasal polyps score (NPS) at Week 52 - ITT population

		Dupilumab	
NPS	Placebo (N=153)	300mg q2w-q4w (N=145)	300mg q2w (N=150)
Baseline			
Number	152	145	149
Mean (SD)	5.96 (1.21)	6.29 (1.20)	6.07 (1.22)
Median	6.00	6.00	6.00
Q1 : Q3	5.50 : 7.00	5.50 : 7.00	5.50 : 7.00
Min : Max	2.0 : 8.0	3.0 : 8.0	1.5 : 8.0
Week 52			
Number	142	137	141
Mean (SD)	6.10 (1.52)	4.12 (1.96)	3.76 (2.20)
Median	6.00	4.00	4.00
Q1 : Q3	5.50 : 7.50	3.00 : 5.50	2.00 : 5.50
Min : Max	0.0 : 8.0	0.0 : 8.0	0.0 : 8.0
Change from baseline			
Number	142	137	141
Mean (SD)	0.12 (1.20)	-2.20 (1.88)	-2.30 (1.97)
Median	0.00	-2.00	-2.00
Q1 : Q3	-0.50 : 1.00	-3.50 : -0.50	-4.00 : -0.50
Min : Max	-4.0 : 3.5	-7.5 : 2.0	-6.0 : 2.0
LS Mean (SE) [a]	0.15 (0.15)	-2.06 (0.15)	-2.24 (0.15)
LS Mean Diff vs. placebo (95% CI) [a]		-2.21 (-2.59, -1.83)	-2.40 (-2.77, -2.02)
P-value vs. placebo [a]		<.0001	<.0001

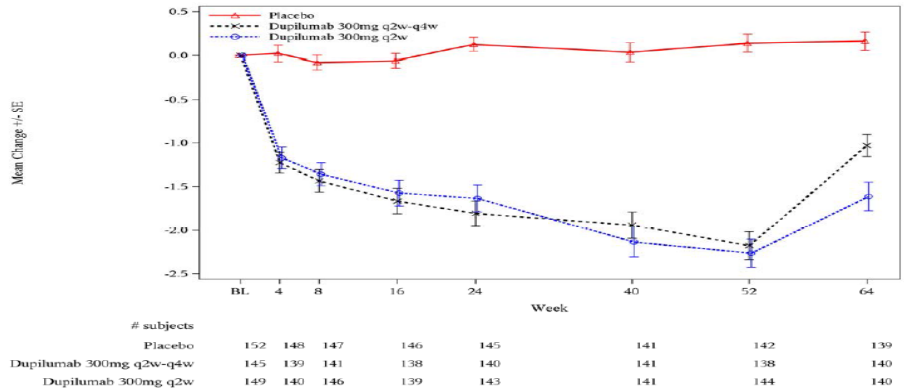
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 52 include patients after WOCF at Week 52, and patients whose Week 52 values were imputed by MI were excluded from the descriptive analysis.

A greater numerical improvement was seen in NPS in patients who stayed on dupilumab 300 mg q2w compared with the patients who were switched to dupilumab 300 mg q4w at Week 24. The LS mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -0.53 and -0.31, respectively, with an LS mean difference of -0.22 (95% CI: -0.50 to 0.07).

LS mean change from baseline in bilateral nasal polyps score (NPS) by visit up to Week 52 - ITT population



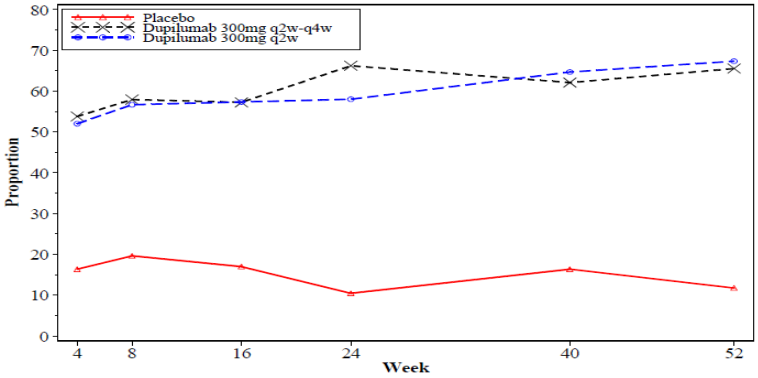
Updated Figure of mean change from baseline in bilateral nasal polyps score (NPS) by visit – ITT population



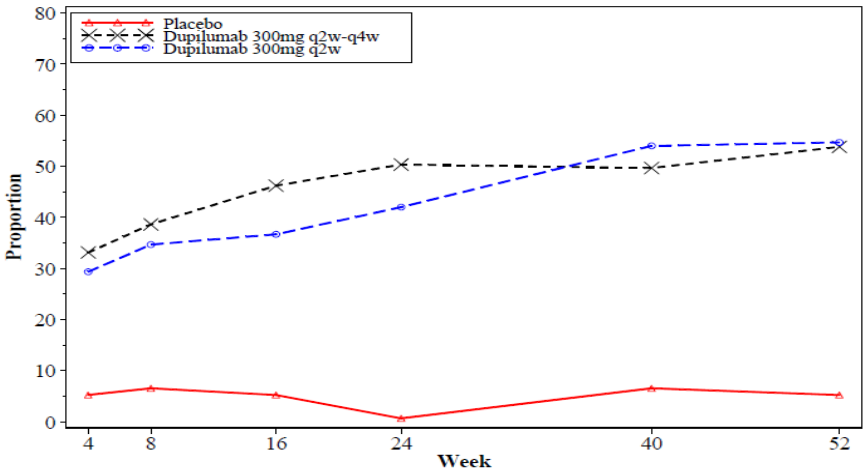
Other secondary endpoint: Responder analysis

Responder analyses evaluated the percentage of patients with a change from baseline in bilateral endoscopic NPS ≥1 point or ≥2 points at Week 24. A higher percentage of patients had a ≥1 point and ≥2 point improvement in NPS in the dupilumab 300 mg q2w group (pooled Arm A+B) compared with the placebo[(62.0% versus 10.5%, nominal p<0.0001) and (46.1% versus 0.7%, nominal p<0.0001) respectively]. The improvement in NPS was rapid and a difference was seen as early as assessment at Week 4. The improvement continued through week 24 and week 52, resulting in a higher percentage of responders at Week 52 for both dupilumab groups than that observed in week 24.

Proportion of patients with NPS improvement from baseline >=1 by visit up to Week 52 - ITT populati



Proportion of patients with NPS improvement from baseline >=2 by visit up to Week 52 - ITT population



- **CHANGE FROM BASELINE IN NASAL CONGESTION/OBSTRUCTION (NC)**

Nasal congestion/obstruction was assessed by the patient on a daily basis using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) as a reflective assessment using a 24-hour recall period.

Primary analysis: Change from baseline in nasal congestion/obstruction at Week 24

The dupilumab treatment group shows a statistically significant improvement in the mean NC symptom score compared with placebo at Week 24, with an LS mean change from baseline to Week 24 of -1.25 for the 300 mg q2w dupilumab group (pooled Arm A+B) and -0.38 for the placebo group (LS mean difference versus placebo: -0.87 with 95% CI: -1.03 to -0.71; p<0.0001).

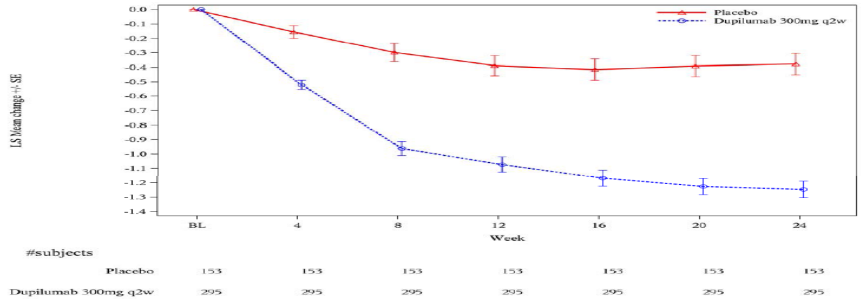
Primary approach: Change from baseline in nasal congestion/obstruction (NC) at Week 24 - ITT population

NC	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	153	295
Mean (SD)	2.38 (0.54)	2.46 (0.61)
Median	2.29	2.71
Q1 : Q3	2.00 : 3.00	2.00 : 3.00
Min : Max	1.0 : 3.0	0.0 : 3.0
Week 24		
Number	147	289
Mean (SD)	2.02 (0.77)	1.19 (0.90)
Median	2.00	1.00
Q1 : Q3	1.61 : 2.75	0.31 : 2.00
Min : Max	0.0 : 3.0	0.0 : 3.0
Change from baseline		
Number	147	289
Mean (SD)	-0.36 (0.73)	-1.28 (0.95)
Median	-0.05	-1.14
Q1 : Q3	-0.85 : 0.00	-2.00 : -0.52
Min : Max	-2.9 : 1.1	-3.0 : 1.0
LS Mean (SE) [a]	-0.38 (0.07)	-1.25 (0.06)
LS Mean Diff vs. placebo (95% CI) [a]		-0.87 (-1.03, -0.71)
P-value vs. placebo [a]		<.0001

Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

The improvement in NC score was rapid with an onset of a difference observed at Week 4 with an LS mean change from baseline to Week 4 of -0.52 for the 300 mg q2w dupilumab group [pooled Arm A+B] and -0.16 for the placebo group (LS mean difference versus placebo: -0.37 with 95% CI: -0.46 to -0.27; nominal p<0.0001). The NC symptom score showed continued improvement through Week 24.

LS mean change from baseline in nasal congestion/obstruction (NC) by month up to Week 24 - ITT population



Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.

Sensitivity analyses using the MMRM approach, Pattern mixture model (PMM) and as-observed analysis showed similar results as the primary WOCF/MI analysis.

Key secondary efficacy endpoint: Change from baseline at Week 52 (Multiplicity controlled)

Dupilumab 300 mg q2w demonstrated a statistically significant improvement in the mean NC symptom score compared with placebo at Week 52 (LS mean difference in the 300 mg q2w dupilumab group [Arm A] versus placebo: -0.98 with 95% CI: -1.17 to -0.79; p<0.0001).

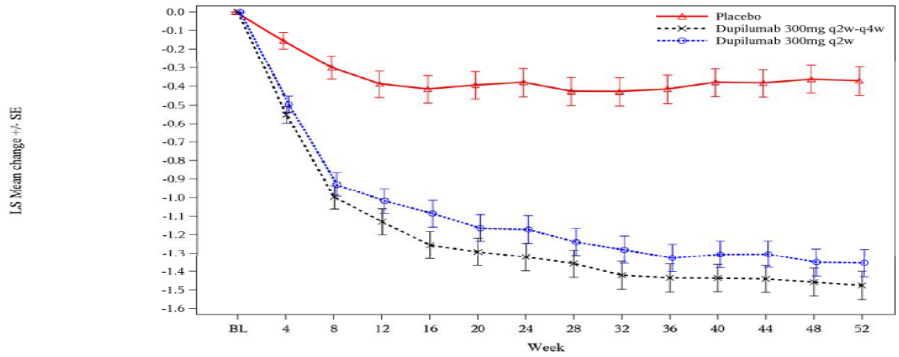
Change from baseline in nasal congestion/obstruction (NC) at Week 52 - ITT population

		Dupilumab	
NC	Placebo (N=153)	300mg q2w-q4w (N=145)	300mg q2w (N=150)
Baseline			
Number	153	145	150
Mean (SD)	2.38 (0.54)	2.44 (0.59)	2.48 (0.62)
Median	2.29	2.57	2.86
Q1 : Q3	2.00 : 3.00	2.00 : 3.00	2.00 : 3.00
Min : Max	1.0 : 3.0	0.3 : 3.0	0.0 : 3.0
Week 52			
Number	144	142	145
Mean (SD)	2.04 (0.78)	0.95 (0.84)	1.10 (0.92)
Median	2.00	1.00	1.00
Q1 : Q3	1.62 : 2.91	0.00 : 1.42	0.13 : 2.00
Min : Max	0.0 : 3.0	0.0 : 3.0	0.0 : 3.0
Change from baseline			
Number	144	142	145
Mean (SD)	-0.34 (0.72)	-1.50 (0.93)	-1.39 (0.98)
Median	-0.04	-1.68	-1.43
Q1 : Q3	-0.87 : 0.00	-2.04 : -1.00	-2.00 : -0.62
Min : Max	-2.9 : 1.0	-3.0 : 1.0	-3.0 : 1.0
LS Mean (SE) [a]	-0.37 (0.08)	-1.48 (0.08)	-1.35 (0.07)
LS Mean Diff vs. placebo (95% CI) [a]		-1.10 (-1.29, -0.91)	-0.98 (-1.17, -0.79)
P-value vs. placebo [a]		<.0001	<.0001

[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with change from baseline at the corresponding visit as the response variable, and the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI.

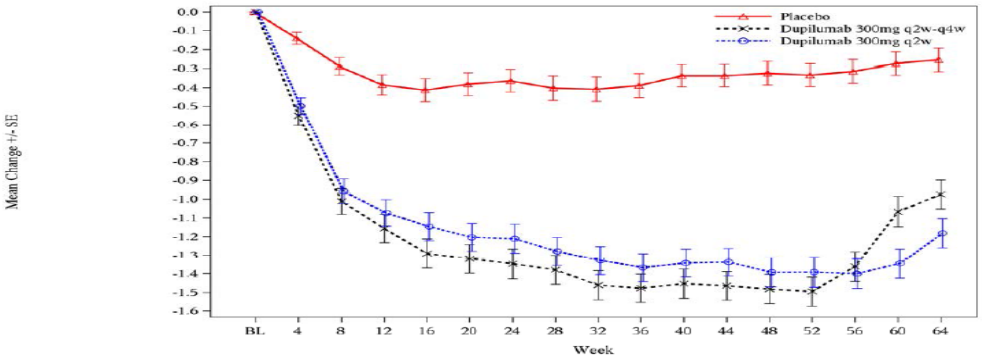
The improvement in NC score was similar for patients who stayed on dupilumab 300 mg q2w compared with those who were switched to 300 mg q4w at Week 24. The LS mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -0.16 and -0.17, respectively, with an LS mean difference of 0.01 (95% CI: -0.12 to 0.14).

LS mean change from baseline in nasal congestion/obstruction (NC) by month up to Week 52 - ITT population



#subjects	BL	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	153	153	153	153	153	153	153	153	153	153	153	153	153	153
Dupilumab 300mg q2w-q4w	145	145	145	145	145	145	145	145	145	145	145	145	145	145
Dupilumab 300mg q2w	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Updated Figure of mean change from baseline in nasal congestion/obstruction (NC) by month - ITT population



# subjects	BL	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
Placebo	153	152	152	150	150	148	147	145	145	145	145	144	144	144	142	140	138
Dupilumab 300mg q2w-q4w	145	145	145	145	144	143	143	143	142	141	143	142	142	142	140	136	136
Dupilumab 300mg q2w	150	150	149	147	147	146	146	146	146	145	146	146	145	145	144	142	143

<u>Other secondary endpoint: Proportion of patients with improvement in nasal congestion/obstruction severity grade at Week 24</u>

For this analysis, the baseline NC score was the median of the daily score in the 7 days prior to randomization.

Similar to the results observed for the primary analysis, dupilumab 300 mg q2w increased the proportion of patients with improvement from baseline in NC score at Week 24 compared with the placebo group.

<u>Other secondary endpoint: Nasal polyps score and nasal congestion/obstruction: Responder analysis</u>

For the purpose of this responder analysis evaluating the percentage of patients with improvement in both NPS and NC, improvement in NPS was considered a decrease from baseline ≥1 point and improvement in NC score was considered a decrease from baseline ≥0.5 points.

At Week 24, a higher percentage of patients showed improvement in both NPS and NC in the dupilumab 300 mg q2w group (pooled Arm A+B) compared with placebo (52.2% versus 5.2%, nominal p<0.0001).

At Week 52, the proportion of patients showing improvement in both NPS and NC score was greater in the dupilumab 300 mg q2w group (Arm A) compared with the placebo group (58.7% versus 9.2%, nominal p<0.0001). Similar results were seen for the patients who were switched to dupilumab 300 mg q4w at Week 24. The proportion of patients showing improvement in both score

was greater in the dupilumab 300 mg q2w-q4w group (Arm B) compared with placebo at Week 52 (57.9% versus 9.2%, nominal p<0.0001).

SECONDARY ENDPOINTS

- **Sinus opacification CT scan score (Lund-Mackay score)**

Key secondary efficacy endpoint: Change from baseline to Week 24 (Multiplicity controlled)

A statistically significant improvement in the mean total sinus opacification CT scan score (LMK) is seen in the dupilumab treatment arm compared to placebo, which showed no improvement in sinus disease at Week 24 (LS mean difference in the dupilumab 300 mg q2w group [pooled Arm A+B] versus placebo: -5.13 with 95% CI: -5.80 to -4.46; p<0.0001).

Primary approach: Change from baseline in sinus opacification CT scan score (Lund-Mackay score) at Week 24 - ITT population

LMK	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	150	289
Mean (SD)	17.65 (3.76)	18.12 (3.75)
Median	17.00	19.00
Q1 : Q3	15.00 : 21.00	15.00 : 21.00
Min : Max	6.0 : 24.0	4.0 : 24.0
Week 24		
Number	142	282
Mean (SD)	17.73 (3.81)	12.86 (3.87)
Median	17.00	14.00
Q1 : Q3	15.00 : 21.00	11.00 : 15.00
Min : Max	6.0 : 24.0	2.0 : 24.0
Change from baseline		
Number	142	282
Mean (SD)	0.11 (1.88)	-5.23 (4.42)
Median	0.00	-5.00
Q1 : Q3	0.00 : 1.00	-8.00 : -1.00
Min : Max	-7.0 : 6.0	-17.0 : 8.0
LS Mean (SE) [a]	-0.09 (0.31)	-5.21 (0.24)
LS Mean Diff vs. placebo (95% CI) [a]		-5.13 (-5.80, -4.46)
P-value vs. placebo [a]		<.0001

Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Sensitivity analyses show similar results as the primary WOCF/MI analysis.

Other secondary efficacy endpoints: Change from baseline to Week 52

Dupilumab 300 mg q2w demonstrated a clinically meaningful improvement in sinus opacification CT scan score (LMK) compared with placebo at Week 52 (LS mean difference in the dupilumab 300 mg q2w group [Arm A] versus placebo at Week 52: -6.94 with 95% CI: -7.87 to -6.01; nominal p<0.0001). The LS mean change from baseline to Week 52 for the dupilumab 300 mg q2w group was greater than that observed at Week 24, indicating continued improvement through 52 weeks. An improvement was also observed for patients who switched at Week 24 from 300 mg q2w to 300 mg q4w (Arm B). However, a greater numerical improvement was seen in sinus opacification CT scan score (LMK) in patients who stayed on dupilumab 300 mg q2w compared with those who switched to dupilumab 300 mg q4w from Week 24 to Week 52. The LS mean difference from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -1.37 and -0.62, respectively, with an LS mean difference of -0.75 (95% CI: -1.52 to 0.01).

- **Disease specific daily symptom assessment and total symptom score (TSS)**

Key secondary efficacy endpoint: Change from baseline to Week 24 (Multiplicity controlled)

The improvement in mean TSS in the dupilumab group compared to placebo was statistical significant at week 24 (LS mean difference in the dupilumab 300 mg q2w group [pooled Arm A+B] versus placebo: -2.44 with 95% CI: -2.87 to -2.02; p<0.0001).

Change from baseline in total symptom score (TSS) at Week 24 - ITT population

TSS	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	153	295
Mean (SD)	7.08 (1.38)	7.30 (1.48)
Median	7.00	7.57
Q1 : Q3	6.07 : 8.14	6.43 : 8.50
Min : Max	2.8 : 9.0	1.5 : 9.0
Week 24		
Number	145	289
Mean (SD)	6.08 (1.97)	3.77 (2.44)
Median	6.16	3.45
Q1 : Q3	5.02 : 7.50	1.78 : 5.81
Min : Max	0.0 : 9.0	0.0 : 9.0
Change from baseline		
Number	145	289
Mean (SD)	-1.03 (1.66)	-3.54 (2.47)
Median	-0.55	-3.75
Q1 : Q3	-2.02 : 0.00	-5.36 : -1.67
Min : Max	-7.0 : 2.0	-8.8 : 4.0
LS Mean (SE) [a]	-1.00 (0.20)	-3.45 (0.15)
LS Mean Diff vs. placebo (95% CI) [a]		-2.44 (-2.87, -2.02)
P-value vs. placebo [a]		<.0001

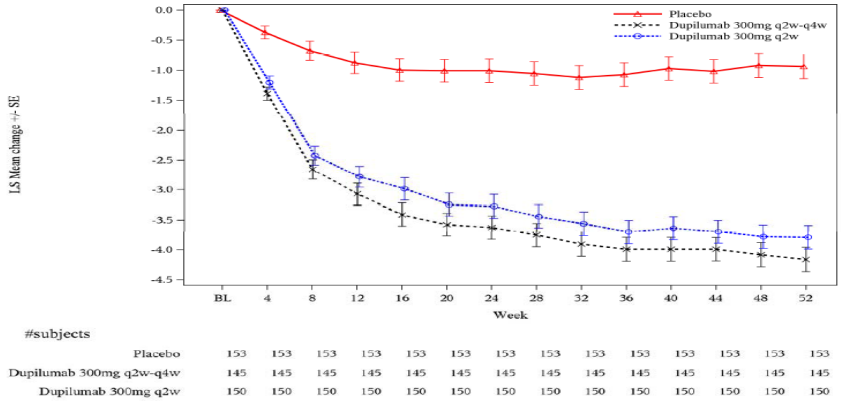
Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Consistent with the observations in the individual symptoms (for NC, loss of smell, and rhinorrhea), the improvement in TSS score was rapid with an onset of a difference versus placebo observed as early as the first post-baseline monthly average score at Week 4 and improved through week 24.

Other secondary efficacy endpoints: Change from baseline to Week 52

Dupilumab 300 mg q2w demonstrated a substantial improvement in the mean TSS compared with placebo at Week 52 (LS mean difference in the 300 mg q2w dupilumab group [Arm A] versus placebo at Week 52: -2.85 with 95% CI: -3.35 to -2.35; nominal p<0.0001). The LS mean change was greater than in week 24, indicating continued improvement. An improvement was seen for patients on dupilumab 300 mg q2w and those who switched to dupilumab 300 mg q4w from Week 24 to Week 52. The LS mean difference from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w arm (Arm B) was -0.50 and -0.57, respectively with an LS mean difference of 0.07 (95% CI: -0.26 to 0.41).

LS mean change from baseline in TSS by month up to Week 52 - ITT population



- **Smell test: University of Pennsylvania Smell Identification Test (UPSIT)**

Key secondary efficacy endpoint: Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab demonstrated a statistically significant improvement in mean UPSIT compared with placebo at Week 24 (LS mean difference in the dupilumab 300 mg q2w group [pooled Arm A+B] versus placebo: 10.52, with 95% CI: 8.98 to 12.07 (p<0.0001).

Change from baseline in UPSIT at Week 24 - ITT population

UPSIT	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	150	287
Mean (SD)	13.78 (8.31)	13.53 (7.88)
Median	11.00	11.00
Q1 : Q3	10.00 : 17.00	9.00 : 16.00
Min : Max	0.0 : 33.0	0.0 : 40.0
Week 24		
Number	145	280
Mean (SD)	13.30 (7.96)	23.89 (9.21)
Median	11.00	25.00
Q1 : Q3	9.00 : 17.00	16.00 : 31.00
Min : Max	0.0 : 33.0	0.0 : 40.0
Change from baseline		
Number	145	280
Mean (SD)	-0.21 (5.15)	10.28 (10.17)
Median	0.00	10.00
Q1 : Q3	-3.00 : 2.00	1.00 : 18.50
Min : Max	-20.0 : 18.0	-24.0 : 33.0
LS Mean (SE) [a]	-0.81 (0.71)	9.71 (0.56)
LS Mean Diff vs. placebo (95% CI) [a]		10.52 (8.98, 12.07)
P-value vs. placebo [a]		<.0001

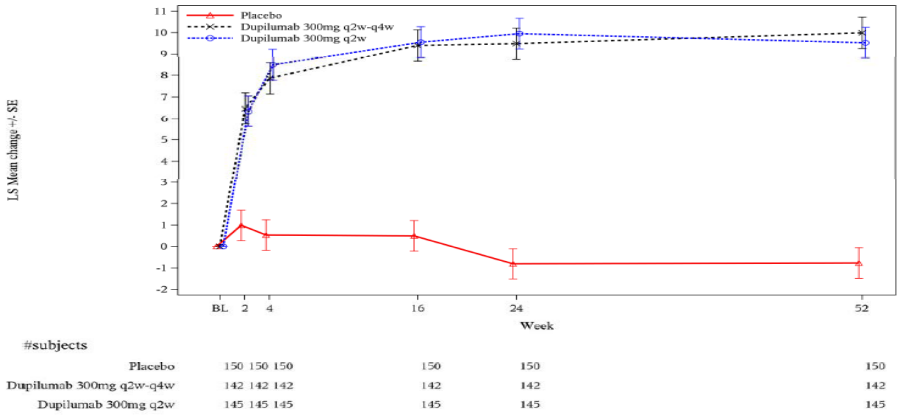
Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

The improvement was rapid, with an LS mean change from baseline to Week 2 of 6.40 for the 300 mg q2w dupilumab group [pooled Arm A+B] and 0.93 for the placebo group (LS mean difference versus placebo: 5.47 with 95% CI: 3.97 to 6.98; nominal p<0.0001) and showed continued improvement through approximately Week 16 at which time a plateau through Week 24 was observed. Of note, In study EFC14280, the proportion of patients with anosmia at Week 24 was reduced from 79.4% to 30% in the dupilumab 300 mg q2w group (pooled Arm A+B) compared with almost no change in the placebo group (76.7 % at baseline and 76.6% at Week 24).

Other secondary efficacy endpoint: Change from baseline to Week 52

At week 52 dupilumab 300 mg q2w demonstrated an improvement in mean UPSIT compared to placebo (LS mean difference in the 300 mg q2w dupilumab group [Arm A] versus placebo at Week 52: 10.30 with 95% CI: 8.50 to 12.10 (nominal p<0.0001). The LS mean change was similar to the observed change at week 24. The maximum increase in UPSIT was obtained at Week 16 and plateaued through Week 52. Similar UPSIT scores were seen in patients on dupilumab 300 mg q2w compared to the patients who were switched to dupilumab 300 mg q4w from Week 24 to Week 52. The LS mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -0.54 and +0.31, respectively, with an LS mean difference of -0.85 (95% CI: -2.06 to 0.37).

LS mean change from baseline in UPSIT score by visit up to Week 52 - ITT population



Other secondary efficacy endpoint: Patients with anosmia by UPSIT scores

At Week 24, the proportion of patients with anosmia was reduced from 79.4% to 30.0% in the dupilumab 300 mg q2w group (pooled Arm A+B) with essentially no change in the placebo group (76.7% to 76.6%). 28.9% of patients in the dupilumab group had UPSIT scores in either the mild microsmia or normal smell perception range at week 24. In contrast, in the placebo group, 9 patients had mild microsmia or normal smell at baseline and only 5 (3.4%) had UPSIT scores in the mild microsmia or normal smell perception range at the same timepoint. Similar were the results at week 52, where the proportion of patients with anosmia was lower in both the dupilumab 300 mg q2w and 300 mg q2w-q4w groups compared with the placebo group (28.1% and 27.5% for the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, versus 75.4% for the placebo group).

- **Decreased/loss of sense of smell**

Key secondary efficacy endpoint: Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab demonstrated a statistically significant improvement in mean daily assessed loss of smell score compared with placebo at Week 24 (LS mean difference in the dupilumab 300 mg q2w group [pooled Arm A+B] versus placebo: -0.98 with 95% CI: -1.15 to -0.81; p<0.0001).

Change from baseline in daily self-reported loss of smell at Week 24 - ITT population

Loss of smell	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	153	295
Mean (SD)	2.72 (0.52)	2.77 (0.53)
Median	3.00	3.00
Q1 : Q3	2.71 : 3.00	3.00 : 3.00
Min : Max	0.0 : 3.0	0.0 : 3.0
Week 24		
Number	147	289
Mean (SD)	2.49 (0.79)	1.55 (1.02)
Median	3.00	1.39
Q1 : Q3	2.00 : 3.00	1.00 : 2.24
Min : Max	0.0 : 3.0	0.0 : 3.0
Change from baseline		
Number	147	289
Mean (SD)	-0.23 (0.56)	-1.21 (1.02)
Median	0.00	-1.00
Q1 : Q3	-0.19 : 0.00	-2.00 : -0.04
Min : Max	-3.0 : 1.1	-3.0 : 1.9
LS Mean (SE) [a]	-0.23 (0.08)	-1.21 (0.06)
LS Mean Diff vs. placebo (95% CI) [a]		-0.98 (-1.15, -0.81)
P-value vs. placebo [a]		<.0001

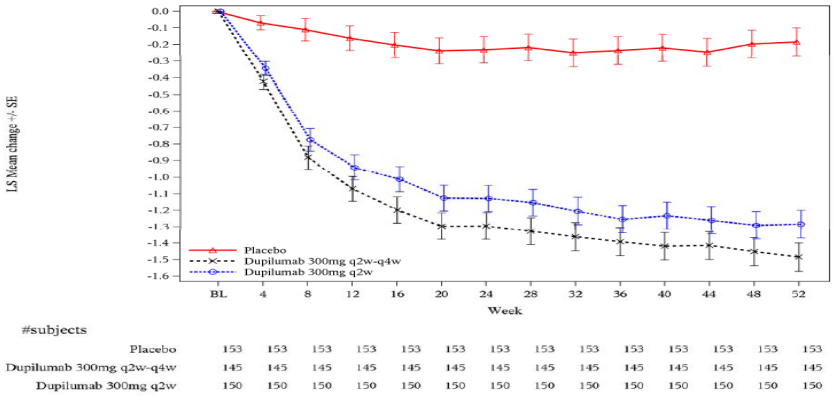
Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

The improvement was rapid with an onset of a difference versus placebo observed as early as the first post-baseline monthly average score at Week 4 with an LS mean change from baseline to Week 4 of -0.38 for the 300 mg q2w dupilumab group [pooled Arm A+B] and -0.07 for the placebo group (LS mean difference versus placebo: -0.31 with 95% CI: -0.41 to -0.22; nominal p<0.0001). The sense of smell score showed continued improvement through Week 24.

Other secondary efficacy endpoints: Change from baseline to Week 52

Similar to the key secondary endpoint at week 24 improvement in the mean daily self-reported loss of smell score in the dupilumab groups was demonstrated compared with placebo at Week 52 (LS mean difference in the 300 mg q2w dupilumab group [Arm A] versus placebo at Week 52: -1.10 with 95% CI: -1.31 to -0.89; nominal p<0.0001). The maximum effect was obtained at approximately Week 36 and sustained through Week 52. A similar improvement in loss of smell was observed in both dupilumab groups (dupilumab 300 mg q2w and dupilumab 300 mg q2w/q4w). The LS mean change from Week 24 to Week 52 in the dupilumab 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -0.14 and -0.20, respectively with an LS mean difference of 0.06 (95% CI: -0.09 to 0.20).

LS mean change from baseline in daily assessed loss of smell by month up to Week 52 - ITT population



- **22-Item sino-nasal outcome test (SNOT-22)**

Key secondary efficacy endpoint: Change from baseline to Week 24 (Multiplicity controlled)

Dupilumab demonstrated a statistically significant improvement in mean SNOT-22 total score compared with placebo at Week 24 (LS mean difference in the dupilumab group [pooled Arm A+B] versus placebo: -17.36 with 95% CI: -20.87 to -13.85; p<0.0001).

Change from baseline in SNOT-22 at Week 24 - ITT population

SNOT-22	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Baseline		
Number	152	292
Mean (SD)	53.48 (21.85)	51.02 (20.37)
Median	51.50	51.00
Q1 : Q3	37.50 : 69.50	36.50 : 64.50
Min : Max	11.0 : 110.0	8.0 : 108.0
Week 24		
Number	145	282
Mean (SD)	42.16 (23.26)	23.89 (18.77)
Median	39.00	20.00
Q1 : Q3	22.00 : 60.00	10.00 : 33.00
Min : Max	2.0 : 101.0	0.0 : 96.0
Change from baseline		
Number	145	282
Mean (SD)	-10.94 (19.29)	-27.32 (21.88)
Median	-9.00	-26.00
Q1 : Q3	-21.00 : 0.00	-39.00 : -12.00
Min : Max	-85.0 : 42.0	-103.0 : 33.0
LS Mean (SE) [a]	-10.40 (1.61)	-27.77 (1.26)
LS Mean Diff vs. placebo (95% CI) [a]		-17.36 (-20.87, -13.85)
P-value vs. placebo [a]		<.0001

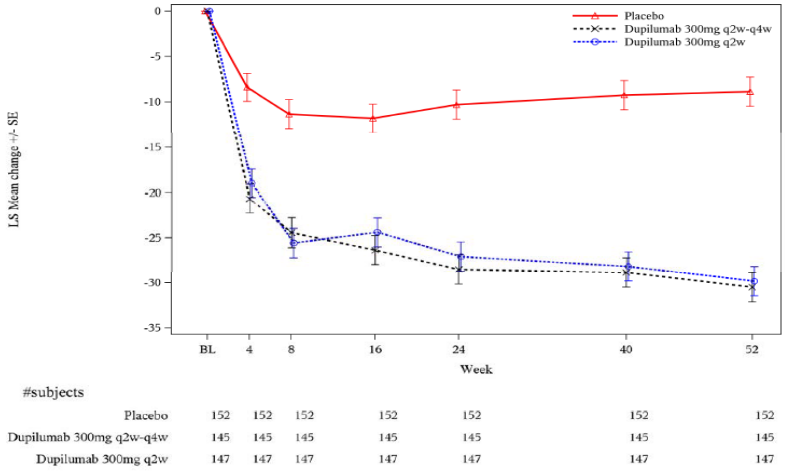
Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.
Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

The improvement in SNOT-22 total score was rapid and observed as early as Week 4 with an LS mean change from baseline to Week 4 of -19.77 for the 300 mg q2w dupilumab group [pooled Arm A+B] and -8.35 for the placebo group (LS mean difference versus placebo: -11.41 with 95% CI: -14.78 to -8.05; nominal p<0.0001). The SNOT-22 total score showed continued improvement through Week 24.

<u>Other secondary efficacy endpoint: Change from baseline to Week 52</u>

In line with the key secondary endpoint Dupilumab 300 mg q2w demonstrated a statistically significant improvement in mean SNOT-22 compared with placebo at Week 52 (LS mean difference in the 300 mg q2w dupilumab group [Arm A] versus placebo: -20.96 with 95% CI: -25.03 to -16.89; p<0.0001). The LS mean change at Week 52 for the dupilumab 300 mg q2w group was greater than that observed at Week 24, indicating continued improvement through 52. Similar improvement was observed in patients who stayed on dupilumab 300 mg q2w compared with those who were switched to dupilumab 300 mg q4w at Week 24. The LS mean change from Week 24 to Week 52 in the 300 mg q2w group (Arm A) and 300 mg q2w-q4w group (Arm B) was -2.84 and -2.45, respectively, with an LS mean difference of -0.39 (95% CI: -2.90 to 2.12).

LS mean change from baseline in SNOT-22 total score by visit up to Week 52 – ITT population



Other secondary efficacy endpoint: Responder analysis

At Week 24, a higher percentage of patients had a ≥8.9 point decrease in SNOT-22 total score in the dupilumab 300 mg q2w group (pooled Arm A+B) compared with the placebo group (73.9% versus 39.9%, nominal p<0.0001).

At Week 52, the proportion of patients meeting the MCID was greater in the dupilumab 300 mg q2w group (Arm A) compared with the placebo group (75.3% versus 30.1%, nominal p<0.0001). Likewise, for the patients who were switched to 300 mg q4w at Week 24, the proportion of patients showing MCID improvement was greater in the dupilumab 300 mg q2w-q4w group (Arm B) compared with the placebo group at Week 52 (76.6% versus 30.1%, nominal p<0.0001).

- **Proportion of patients requiring rescue treatment**

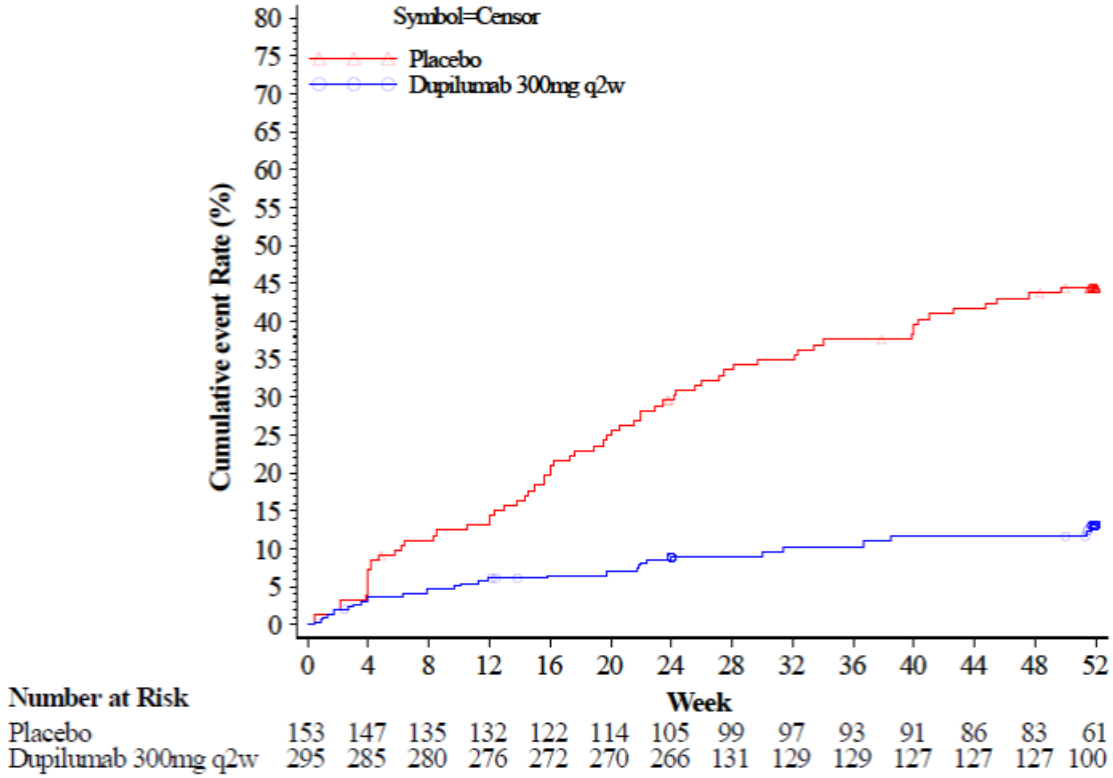
The proportion of patients who required rescue treatment with SCS or NP surgery during the treatment period was lower in the dupilumab 300 mg group (pooled Arm A for 52 weeks + Arm B for first 24 weeks; q2w dosing) compared with the placebo group during the 52 week treatment period (Kaplan-Meier estimate at Week 52: 13.1% versus 44.4%, with a hazard ratio [95% CI] of 0.238 [0.156 to 0.364], nominal p<0.0001) (Table 48).
The difference between the dupilumab group and placebo group was apparent from Week 4 through the end of the study period (Figure 26).

Table 48 - Proportion of patients with SCS use and/or NP surgery during treatment period - ITT population

	Placebo (N=153)	Dupilumab 300mg q2w (N=295)
Number of patients		
With SCS use/NP surgery	67 (43.8%)	32 (10.8%)
Kaplan-Meier estimates for probability of a patient with >=1 event (95% CI) up to		
16 weeks	0.210 (0.149 to 0.278)	0.065 (0.040 to 0.097)
24 weeks	0.296 (0.225 to 0.369)	0.089 (0.060 to 0.125)
40 weeks	0.396 (0.318 to 0.473)	0.116 (0.079 to 0.162)
52 weeks	0.444 (0.363 to 0.521)	0.131 (0.090 to 0.180)
HR, 95% CI vs placebo [a]		0.238 (0.156, 0.364)
P-value vs. placebo [a]		<.0001

Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
[a] HR: hazard ratio, derived from Cox proportional hazard model with the event of first SCS use and/or NP surgery (actual or planned, whichever is earlier) as the response variable, and treatment, asthma/NSAID-ERD status, prior surgery history and region (pooled countries) as covariates.
PGM=PRODOPS/SAR231893/EFC14280/CSR/REPORT/PGM/eff_time2event_i_t.sas
OUT=REPORT/OUTPUT/eff_time2event_scsnp_i_t_i.rtf (01DEC2018 - 13:55)

Figure 26 – Kaplan-Meier curve for time to first SCS use/NP surgery during treatment period - ITT population



Dupilumab 300 mg q2w: pooled A and B arms. Arm A :300 mg q2w. Arm B : 300mg q2w-q4w.
PGM=PRODOPS/SAR231893/EFC14280/CSR/REPORT/PGM/eff_event_km_i_g.sas OUT=REPORT/OUTPUT/eff_event_km_scsnp_i_g_i.rtf (01DEC2018 - 14:05)

- **Proportion of patients requiring rescue treatment – Pooled Study EFC14146 and EFC14280 (controlled for multiplicity)**

Since the assumption for the number of patients requiring SCS or NP surgery rescue treatment for the sample size calculation was much lower than the observed number, the primary multiplicity controlled analysis of the proportion of patients requiring rescue treatment was planned in the pooled analysis of the 2 pivotal CRSwNP studies, the current study and EFC14146.
In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with dupilumab resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure8). The proportion of patients who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The mean individual annualised prescribed total dose of systemic corticosteroids (in mg) during the treatment period was 71% lower in the pooled dupilumab group compared with the pooled placebo group (60.5 [531.3] mg versus 209.5 [497.2] mg, respectively). The proportion of patients who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Study EFC14146

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial EFC14146

Title: A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids			
Study identifier	EFC14146		
Design	Randomized, double-blind, placebo-controlled phase III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 4 weeks 48 weeks
Hypothesis	Superiority of dupilumab 300mg q2w compared to placebo with respect to change from baseline at week 24 in NPS and NC (co-primary)		
Treatments groups	Arm A, dupilumab		Dupilumab 300mg q2w, N=120
	Arm B, placebo		Matching Placebo q2w, N=120
Endpoints and definitions ***	Co-Primary endpoints	NC and NPS	Change from baseline at week 24
	Key Secondary	TSS	Change from baseline to TSS at Week 24
	Key Secondary	UPSIT	Change from baseline in UPSIT at Week 24.
	Key Secondary	Loss of smell	Change from baseline in loss of smell daily symptoms at Week 24.

	Key Secondary	SNOT-22	Change from baseline in SNOT-22 at Week 24.
	Key Secondary	LMK	Change from baseline in CT LMK score at Week 24 (this will not be a secondary endpoint for Japan as it is already a co-primary endpoint).
	Key Secondary	OCS rescue or surgery for NP	Proportion of patients with OCS rescue or surgery for NP during the treatment period.
	Secondary	NPS, NC, LMK, TSS, UPSIT, loss of smell, SNOT-22	Change from baseline and time course profiles in NPS, NC, LMK, TSS, UPSIT, daily assessed loss of smell, and SNOT-22 at Week 48
Database lock	05 July 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (11 Dec 2018)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	128	137	
	NPS (LS mean change from baseline)	0.17	-1.89	
	SE	0.15	0.14	
	Number of subject	130	141	
	NC (LS mean change from baseline)	-0.45	-1.34	
	SE	0.07	0.07	

Effect estimate per comparison	Co-Primary endpoint NPS	Comparison groups	Dupilumab vs. Placebo
		Difference	-2.06
		95% CI	(-2.43, -1.69)
		P-value	<0.0001
	Co-Primary endpoint NC	Comparison groups	Dupilumab vs. Placebo
		Difference	-0.89
		95% CI	(-1.07, -0.71)
		P-value	<0.0001
Notes	Regarding the co-primary parameters, NPS and NC, the efficacy of Dupilumab was statistically proven. Additional sensitivity and subgroup analyses were performed for the co-primary endpoints which confirmed the results.		

Analysis description	**Key Secondary analyses**			
Analysis population and time point description	Intent to treat (11 Dec 2018)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	129	141	
	TSS (LS mean)	-1.17	-3.77	

	SE	0.17	0.16	
Effect estimate per comparison	Key secondary endpoint TSS	Comparison groups	Dupilumab vs. Placebo	
		Difference	-2.61	
		95% CI	(-3.04, -2.17)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	130	138	
	UPSIT (LS mean)	0.70	11.26	
	SE	0.71	0.67	
Effect estimate per comparison	Key secondary endpoint UPSIT	Comparison groups	Dupilumab vs. Placebo	
		Difference	10.56	
		95% CI	(8.79, 12.34)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	130	141	
	Loss of smell (LS mean)	-0.29	-1.41	
	SE	0.07	0.07	
Effect estimate per comparison	Key secondary endpoint loss of smell	Comparison groups	Dupilumab vs. Placebo	
		Difference	-1.12	
		95% CI	(-1.31, -0.93)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	128	135	
	SNOT-22 (LS mean)	-9.31	-30.43	
	SE	1.62	1.54	
Effect estimate per comparison	Key secondary endpoint SNOT-22	Comparison groups	Dupilumab vs. Placebo	
		Difference	-21.12	
		95% CI	(-25.17, -17.06)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	127	138	
	LMK (LS mean)	-0.74	-8.18	
	SE	0.37	0.34	
Effect estimate per comparison	Key secondary endpoint LMK	Comparison groups	Dupilumab vs. Placebo	
		Difference	-7.44	
		95% CI	(-8.35, -6.53)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	133	143	

	OCS rescue or surgery for NP (N)	30	10	
	%	22.6%	7.0%	

Effect estimate per comparison	Key secondary endpoint OCS rescue or surgery for NP	Comparison groups	Dupilumab vs. Placebo
		Hazard ratio	0.268
		95% CI	(0.131, 0.549)
		P-value	0.0003
Notes	Regarding the key secondary endpoints, the efficacy of Dupilumab compared to placebo could be demonstrated.		

Summary of Study EFC14280

Table 1. Summary of Efficacy for trial EFC14280

Title: A randomized, double-blind, 52-week, placebo controlled efficacy and safety study of dupilumab, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids			
Study identifier	EFC14280		
Design	Randomized, double-blind, placebo-controlled phase III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 4 weeks 52-64 weeks
Hypothesis	Superiority of dupilumab (combined arms A and B, 300mg q2w) compared to placebo with respect to change from baseline at week 24 in NPS and NC (co-primary)		
Treatments groups	Arm A, dupilumab		Dupilumab 300mg q2w, N=120
	Arm A, dupilumab		Dupilumab 300mg q2w-q4w, N=120
	Arm C, placebo		Placebo, N=120
Endpoints and definitions	Co-Primary endpoints	NC and NPS	Change from baseline at week 24
	Key Secondary	TSS	Change from baseline to TSS at Week 24
	Key Secondary	UPSIT	Change from baseline in UPSIT at Week 24.
	Key Secondary	Loss of smell	Change from baseline in loss of smell daily symptoms at Week 24.
	Key Secondary	SNOT-22	Change from baseline in SNOT-22 at Week 24.
	Key Secondary	LMK	Change from baseline in CT LMK score at Week 24 (this will not be a secondary endpoint for Japan as it is already a co-primary endpoint).
	Key Secondary	OCS rescue or surgery for NP	Proportion of patients with OCS rescue or surgery for NP during the treatment period.
Database lock	29 August 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (12 Jan 2019)		

Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	142	283	

	NPS (LS mean change from baseline)	0.10	-1.71	
	SE	0.14	0.11	
	Number of subject	147	289	
	NC (LS mean change from baseline)	-0.38	-1.25	
	SE	0.07	0.06	

Effect estimate per comparison	Co-Primary endpoint NPS	Comparison groups	Dupilumab vs. Placebo
		Difference	-1.80
		95% CI	(-2.10, -1.51)
		P-value	<0.0001
	Co-Primary endpoint NC	Comparison groups	Dupilumab vs. Placebo
		Difference	-0.87
		95% CI	(-1.03, -0.71)
		P-value	<0.0001
Notes	Regarding the co-primary parameters, NPS and NC, the efficacy of Dupilumab was statistically proven. Additional sensitivity and subgroup analyses were performed for the co-primary endpoints which confirmed the results.		
Analysis description	**Key Secondary analyses**		
Analysis population and time point description	Intent to treat (12 Jan 2019)		

Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	145	289	
	TSS (LS mean)	-1.00	-3.45	
	SE	0.20	0.15	

Effect estimate per comparison	Key secondary endpoint TSS	Comparison groups	Dupilumab vs. Placebo
		Difference	-2.44
		95% CI	(-2.87, -2.02)
		P-value	<0.0001

Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	145	280	
	UPSIT (LS mean)	-0.81	9.71	
	SE	0.71	0.56	

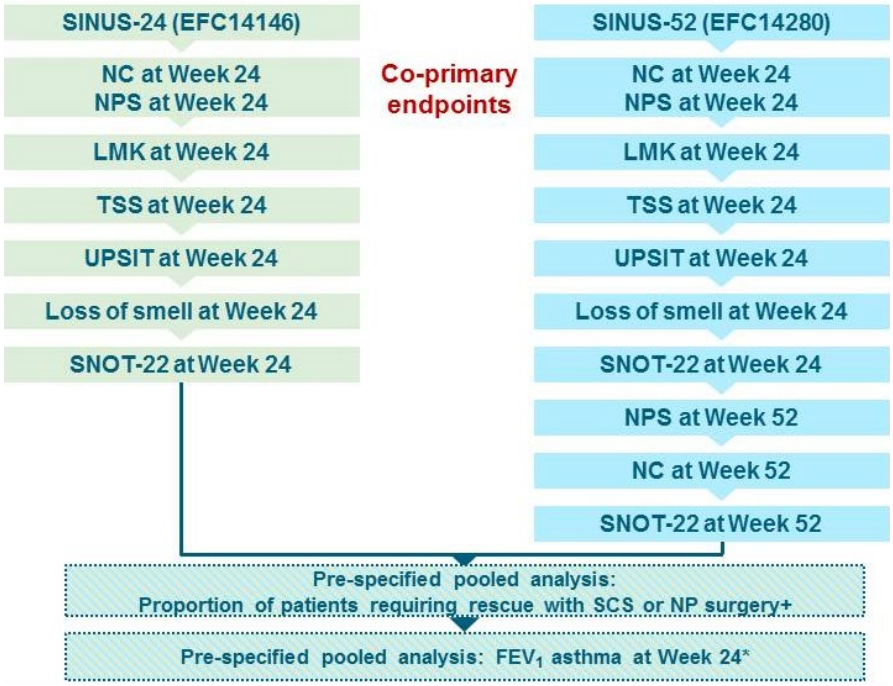
Effect estimate per comparison	Key secondary endpoint UPSIT	Comparison groups	Dupilumab vs. Placebo
		Difference	10.52
		95% CI	(8.98, 12.07)
		P-value	<0.0001

Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	147	289	
	Loss of smell (LS mean)	-0.23	-1.21	

	SE	0.08	0.06	
Effect estimate per comparison	Key secondary endpoint loss of smell	Comparison groups	Dupilumab vs. Placebo	
		Difference	-0.98	
		95% CI	(-1.15, -0.81)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	145	282	
	SNOT-22 (LS mean)	-10.40	-27.77	
	SE	1.61	1.26	
Effect estimate per comparison	Key secondary endpoint SNOT-22	Comparison groups	Dupilumab vs. Placebo	
		Difference	-17.36	
		95% CI	(-20.87, -13.85)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	142	282	
	LMK (LS mean)	-0.09	-5.21	
	SE	0.31	0.24	
Effect estimate per comparison	Key secondary endpoint LMK	Comparison groups	Dupilumab vs. Placebo	
		Difference	-5.13	
		95% CI	(-5.80, -4.46)	
		P-value	<0.0001	
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab	
	Number of subject	153	295	
	OCS rescue or surgery for NP (N)	67	32	
	%	43.8%	10.8%	
Effect estimate per comparison	Key secondary endpoint OCS rescue or surgery for NP	Comparison groups	Dupilumab vs. Placebo	
		Hazard ratio	0.238	
		95% CI	(0.156, 0.364)	
		P-value	<0.0001	
Notes	Regarding the key secondary endpoints, the efficacy of Dupilumab compared to placebo could be demonstrated.			

Analysis performed across trials (pooled analyses and meta-analysis)

Figure 15 - Hierarchical testing order for co-primary and selected secondary endpoints



┼: The pooled analysis for this endpoint (Proportion of patients requiring rescue treatment with SCS or sino-nasal surgery) was tested in the hierarchy only when in both EFC14280 and EFC14146 hierarchies, all endpoints before this one reach statistical significance with p-value ≤0.05.

*: The pooled analysis for this endpoint (Change from baseline in FEV_1 at Week 24) was tested in the hierarchy only when the previous endpoint (the pooled analysis for the proportion of patients requiring rescue treatment with SCS or sino-nasal surgery) achieved statistical significance in this hierarchical testing procedure.

The results presented for both pivotal trials are described below :

Summary of the primary and selected secondary endpoints in the hierarchical testing procedure - ITT population

	EFC14280[b]			EFC14146[c]		
	Placebo (N=153)	Dupilumab 300mg q2w (N=295)	Difference vs. Placebo (p-value)[a]	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	Difference vs. Placebo (p-value)[a]
Primary endpoints (LS Mean change from baseline in)						
Bilateral nasal polyps score (NPS) at Week 24	0.10	-1.71	-1.80 (<.0001)	0.17	-1.89	-2.06 (<.0001)
Nasal congestion/obstruction (NC) at Week 24	-0.38	-1.25	-0.87 (<.0001)	-0.45	-1.34	-0.89 (<.0001)
Key secondary endpoints (LS Mean change from baseline in)						
Lund Mackay score (LMK) at Week 24	-0.09	-5.21	-5.13 (<.0001)	-0.74	-8.18	-7.44 (<.0001)
Total symptom score (TSS) at Week 24	-1.00	-3.45	-2.44 (<.0001)	-1.17	-3.77	-2.61 (<.0001)
Smell test (UPSIT) at Week 24	-0.81	9.71	10.52 (<.0001)	0.70	11.26	10.56 (<.0001)
Loss of smell at Week 24	-0.23	-1.21	-0.98 (<.0001)	-0.29	-1.41	-1.12 (<.0001)
SNOT-22 at Week 24	-10.40	-27.77	-17.36 (<.0001)	-9.31	-30.43	-21.12 (<.0001)

For EFC14280: Dupilumab 300 mg q2w is pooled Arm A and Arm B for comparisons at Week 24, and Arm A only for comparisons at Week 52. Arm A: 300 mg q2w; Arm B: 300 mg q2w-q4w.

[a] For endpoints related to proportion of patients requiring rescue with SCS/NP surgery, the differences are expressed as hazard ratio. For all the other endpoints, the differences are expressed as LS Mean difference.

Comparisons of the efficacy endpoints in each study and in the pooled population - ITT population

	EFC14280[b]			EFC14146[c]			Pooled studies		
	Placebo (N=153)	Dupilumab 300mg q2w (N=295)	Difference vs. Placebo (p-value)[a]	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	Difference vs. Placebo (p-value)[a]	Placebo (N=286)	Dupilumab 300mg q2w (N=438)	Difference vs. Placebo (p-value)[a]
NPS at Week 24	0.10	-1.71	-1.80 (<.0001)	0.17	-1.89	-2.06 (<.0001)	0.12	-1.79	-1.91 (<.0001)
NC at Week 24	-0.38	-1.25	-0.87 (<.0001)	-0.45	-1.34	-0.89 (<.0001)	-0.42	-1.30	-0.88 (<.0001)
LMK at Week 24	-0.09	-5.21	-5.13 (<.0001)	-0.74	-8.18	-7.44 (<.0001)	-0.16	-6.27	-6.12 (<.0001)
TSS at Week 24	-1.00	-3.45	-2.44 (<.0001)	-1.17	-3.77	-2.61 (<.0001)	-1.08	-3.59	-2.52 (<.0001)
Smell test (UPSIT) at Week 24	-0.81	9.71	10.52 (<.0001)	0.70	11.26	10.56 (<.0001)	-0.03	10.54	10.57 (<.0001)
Loss of smell at Week 24	-0.23	-1.21	-0.98 (<.0001)	-0.29	-1.41	-1.12 (<.0001)	-0.26	-1.30	-1.04 (<.0001)
SNOT-22 at Week 24	-10.40	-27.77	-17.36 (<.0001)	-9.31	-30.43	-21.12 (<.0001)	-10.36	-29.22	-18.86 (<.0001)

For EFC14280: Dupilumab 300 mg q2w is pooled Arm A and Arm B for comparisons at Week 24. Arm A: 300 mg q2w; Arm B: 300 mg q2w-q4w.
[a] LS Mean change from baseline in each arm is reported in this table.

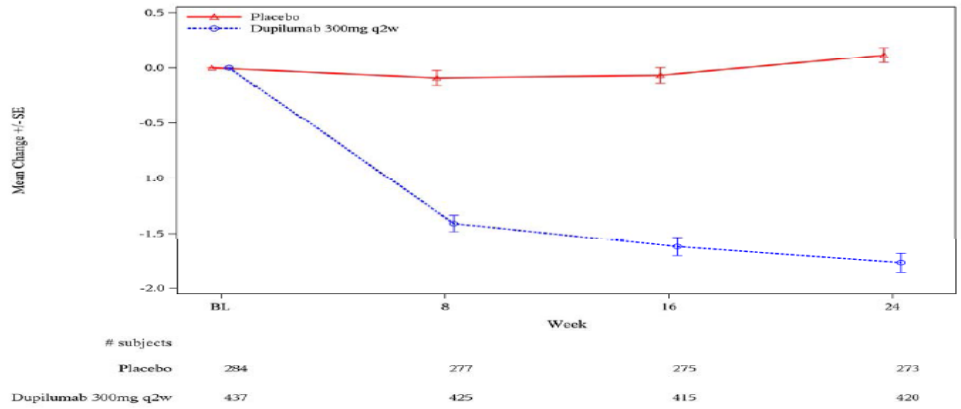
Co-Primary Endpoints

Primary analysis: change from baseline in bilateral nasal polyps score (NPS) at Week 24 - pooled ITT population

NPS	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	284	437
Mean (SD)	5.91 (1.26)	6.00 (1.24)
Median	6.00	6.00
Q1 : Q3	5.00 : 7.00	5.00 : 7.00
Min : Max	2.0 : 8.0	1.5 : 8.0
Week 24		
Number	273	420
Mean (SD)	6.02 (1.31)	4.23 (1.95)
Median	6.00	4.50
Q1 : Q3	5.50 : 7.00	3.00 : 6.00
Min : Max	1.0 : 8.0	0.0 : 8.0
Change from baseline		
Number	273	420
Mean (SD)	0.12 (1.11)	-1.77 (1.79)
Median	0.00	-1.50
Q1 : Q3	-0.50 : 0.50	-3.00 : -0.50
Min : Max	-5.0 : 4.0	-6.5 : 4.5
LS Mean (SE) [a]	0.12 (0.11)	-1.79 (0.09)
LS Mean Diff vs. placebo (95% CI) [a]		-1.91 (-2.14, -1.68)
P-value vs. placebo [a]		<.0001

Data collected after treatment discontinuation were included. In each of the two studies EFC14280 and EFC14146, data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.
[a] Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, regions, and study indicator (EFC14280 = 0 and EFC14146 = 1) as covariates.

Figure of mean change from baseline in bilateral nasal polyps score (NPS) by visit up to Week 24 - pooled ITT population

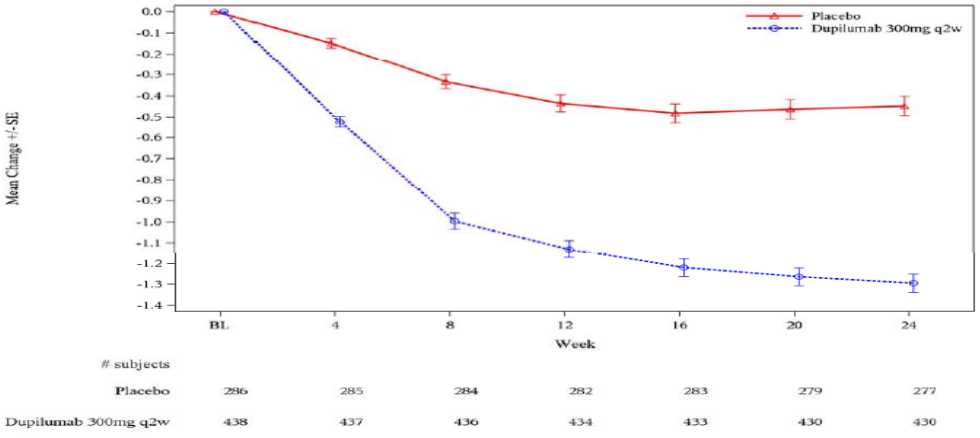


Primary analysis: change from baseline in nasal congestion/obstruction (NC) at Week 24 - pooled ITT population

NC	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	286	438
Mean (SD)	2.41 (0.54)	2.39 (0.60)
Median	2.31	2.43
Q1 : Q3	2.00 : 3.00	2.00 : 3.00
Min : Max	1.0 : 3.0	0.0 : 3.0
Week 24		
Number	277	430
Mean (SD)	1.96 (0.81)	1.11 (0.86)
Median	2.00	1.00
Q1 : Q3	1.39 : 2.75	0.25 : 1.96
Min : Max	0.0 : 3.0	0.0 : 3.0
Change from baseline		
Number	277	430
Mean (SD)	-0.45 (0.76)	-1.29 (0.90)
Median	-0.11	-1.21
Q1 : Q3	-0.96 : 0.00	-2.00 : -0.62
Min : Max	-3.0 : 1.3	-3.0 : 1.0
LS Mean (SE) [a]	-0.42 (0.06)	-1.30 (0.05)
LS Mean Diff vs. placebo (95% CI) [a]		-0.88 (-1.00, -0.76)
P-value vs. placebo [a]		<.0001

Data collected after treatment discontinuation were included. In each of the two studies EFC14280 and EFC14146, data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.
[a] Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, regions, and study indicator (EFC14280 = 0 and EFC14146 = 1) as covariates.

Figure of mean change from baseline in nasal congestion/obstruction (NC) by visit up to Week 24 - pooled ITT population



Secondary endpoints

Primary analysis: change from baseline in total symptom score (TSS) at Week 24 - pooled ITT population

TSS	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	286	438
Mean (SD)	7.18 (1.39)	7.14 (1.45)
Median	7.21	7.21
Q1 : Q3	6.00 : 8.33	6.14 : 8.36
Min : Max	2.3 : 9.0	1.5 : 9.0
Week 24		
Number	274	430
Mean (SD)	6.05 (1.99)	3.57 (2.30)
Median	6.13	3.21
Q1 : Q3	4.98 : 7.57	1.81 : 5.18
Min : Max	0.0 : 9.0	0.0 : 9.0
Change from baseline		
Number	274	430
Mean (SD)	-1.14 (1.69)	-3.59 (2.34)
Median	-0.69	-3.79
Q1 : Q3	-2.21 : 0.00	-5.19 : -1.88
Min : Max	-7.0 : 2.0	-8.9 : 4.0
LS Mean (SE) [a]	-1.08 (0.14)	-3.59 (0.12)
LS Mean Diff vs. placebo (95% CI) [a]		-2.52 (-2.82, -2.21)
P-value vs. placebo [a]		<.0001

Primary analysis: change from baseline in UPSIT at Week 24 - pooled ITT population

UPSIT	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	283	427
Mean (SD)	14.09 (8.30)	13.90 (8.16)
Median	11.00	11.00
Q1 : Q3	10.00 : 17.00	9.00 : 17.00
Min : Max	0.0 : 38.0	0.0 : 40.0
Week 24		
Number	275	418
Mean (SD)	13.90 (8.27)	24.38 (9.32)
Median	11.00	27.00
Q1 : Q3	9.00 : 17.00	17.00 : 32.00
Min : Max	0.0 : 39.0	0.0 : 40.0
Change from baseline		
Number	275	418
Mean (SD)	-0.11 (5.53)	10.40 (10.09)
Median	0.00	10.00
Q1 : Q3	-3.00 : 3.00	1.00 : 19.00
Min : Max	-20.0 : 21.0	-24.0 : 33.0
LS Mean (SE) [a]	-0.03 (0.55)	10.54 (0.48)
LS Mean Diff vs. placebo (95% CI) [a]		10.57 (9.40, 11.74)
P-value vs. placebo [a]		<.0001

Primary analysis: change from baseline in daily assessed loss of smell at Week 24 - pooled ITT population

Loss of smell	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	286	438
Mean (SD)	2.72 (0.52)	2.74 (0.54)
Median	3.00	3.00
Q1 : Q3	2.71 : 3.00	2.86 : 3.00
Min : Max	0.0 : 3.0	0.0 : 3.0
Week 24		
Number	277	430
Mean (SD)	2.50 (0.78)	1.48 (1.01)
Median	3.00	1.08
Q1 : Q3	2.00 : 3.00	1.00 : 2.04
Min : Max	0.0 : 3.0	0.0 : 3.0
Change from baseline		
Number	277	430
Mean (SD)	-0.23 (0.55)	-1.26 (1.02)
Median	0.00	-1.05
Q1 : Q3	-0.19 : 0.00	-2.00 : -0.14
Min : Max	-3.0 : 1.1	-3.0 : 1.9
LS Mean (SE) [a]	-0.26 (0.06)	-1.30 (0.05)
LS Mean Diff vs. placebo (95% CI) [a]		-1.04 (-1.17, -0.91)
P-value vs. placebo [a]		<.0001

Primary analysis: change from baseline in SNOT-22 at Week 24 - pooled ITT population

SNOT-22	Placebo (N=286)	Dupilumab 300mg q2w (N=438)
Baseline		
Number	283	429
Mean (SD)	52.27 (21.11)	50.05 (20.33)
Median	51.00	49.00
Q1 : Q3	36.00 : 67.00	34.00 : 64.00
Min : Max	10.0 : 110.0	8.0 : 108.0
Week 24		
Number	273	417
Mean (SD)	41.38 (23.14)	22.17 (17.77)
Median	39.00	17.00
Q1 : Q3	22.00 : 58.00	9.00 : 31.00
Min : Max	0.0 : 101.0	0.0 : 96.0
Change from baseline		
Number	273	417
Mean (SD)	-10.45 (18.75)	-27.90 (21.40)
Median	-9.00	-26.00
Q1 : Q3	-20.00 : 0.00	-40.00 : -13.00
Min : Max	-85.0 : 42.0	-103.0 : 33.0
LS Mean (SE) [a]	-10.36 (1.24)	-29.22 (1.09)
LS Mean Diff vs. placebo (95% CI) [a]		-18.86 (-21.52, -16.20)
P-value vs. placebo [a]		<.0001

The applicant presented pooled analysis (study EFC14146 and EFC14280) of patients who required rescue treatment with SCS or with sino-nasal surgery. The proportion of patients who required treatment with SCS or sino-nasal surgery during the treatment period was significantly lower in the pooled dupilumab 300 mg q2w group (12.5%) compared with the pooled placebo group (41.8%) across the 52-week treatment period (both are Kaplan-Meier estimates with a Hazard ratio [95% CI] of 0.243 [0.169-0.351], p <0.0001).
Also less patients required rescue sino-nasal surgery or SCS when these treatments were analysed separately.

Clinical studies in special populations

Subgroup analyses were performed by the applicant using the pooled ITT population.

The following subgroup analyses were performed in the study:

- Age group (<65, ≥65 years)
- Gender (Male, Female)
- Region
- Territory
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (<70, ≥70- < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m2)
- Prior NP surgery history (Yes, No)
- Asthma comorbidity (Yes, No)
- Asthma and/or NERD (Yes, No)
- NERD (Yes, No)
- Allergic rhinitis at baseline (Yes, No)
- SCS use during the past 2 years prior to V1 (Yes, No)

Study EFC14146

- **Nasal polyps score (NPS) at Week 24- EFC14146**

No qualitative interactions were observed and no meaningful quantitative treatment-by-subgroup interactions were observed based on age, gender, region, territory, race, ethnicity, weight, BMI, and SCS use in the prior 2 years

Subgroup analyses of the mean change from baseline at Week 24 in bilateral NPS based on disease characteristics at baseline, including prior NP surgery, asthma and/or NSAID-ERD, showed no meaningful treatment-by-subgroup interactions

Figure: Treatment effect on change from baseline in bilateral NPS at Week 24 by demographic subgroups - ITT population- EFC14146

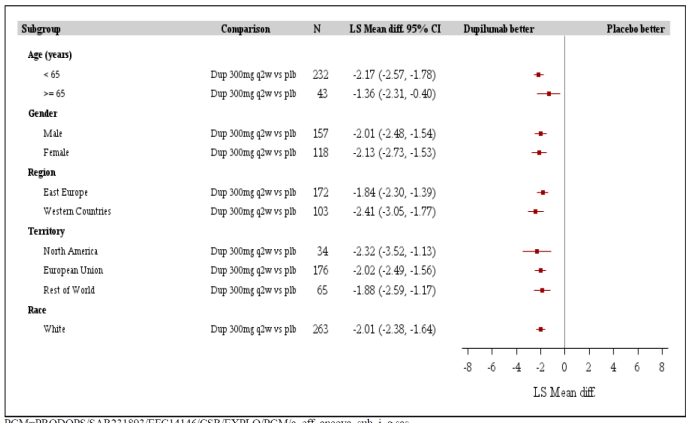


Figure: Treatment effect on change from baseline in bilateral NPS at Week 24 by demographic subgroups - ITT population - EFC14146

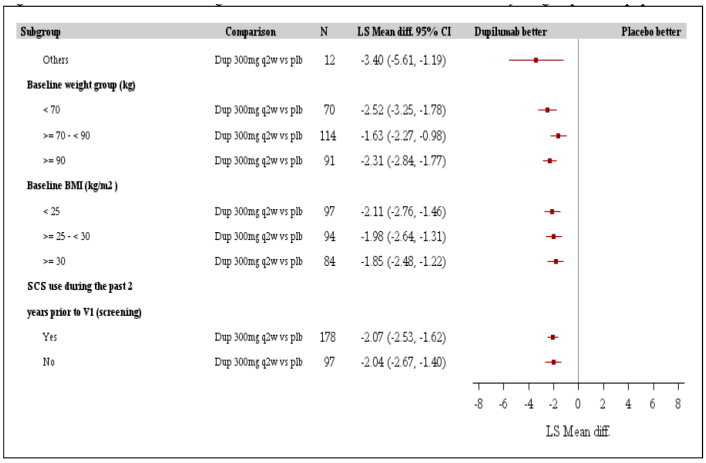
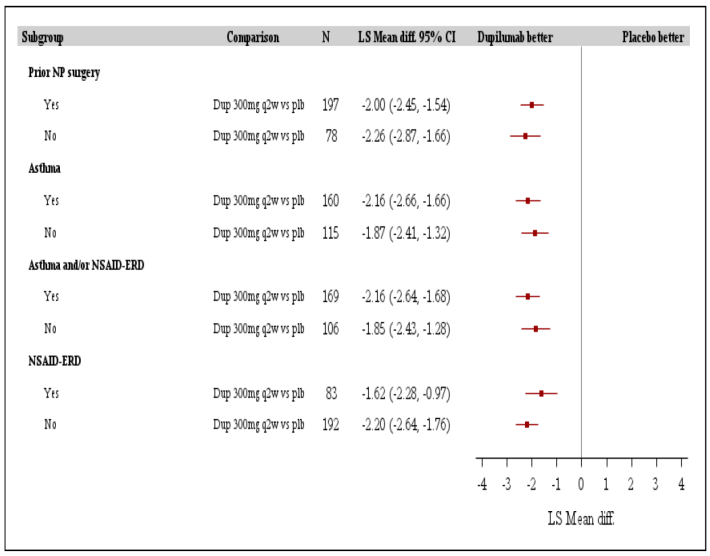


Figure: Treatment effect on change from baseline in bilateral NPS at Week 24 by disease characteristics subgroups - ITT population- EFC14146



- **nasal congestion/obstruction at Week 24- EFC14146**

No meaningful qualitative or quantitative treatment-by-subgroup interactions (p-value<0.05) were observed based on age, gender, region, territory, race, ethnicity, weight, BMI, and SCS use in the prior 2 years

No meaningful treatment-by-subgroup interactions were observed based on prior NP surgery or a history of NSAID-ERD

A quantitative interaction (p<0.05) was detected with regard to the following subgroups:

- **asthma history (nominal p=0.0022)-** magnitude of the treatment effect was greater in the subgroup of patients with history of asthma
- **asthma and/or NSAID-ERD (nominal p=0.0010)-** magnitude of the treatment effect was greater in the subgroup of patients with comorbid asthma and/or NSAID-ERD (LS mean difference versus placebo was -1.12) compared with patients without comorbid asthma and/or NSAID-ERD (LS mean difference versus placebo was -0.52).

Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at Week 24 by demographic subgroups - ITT population

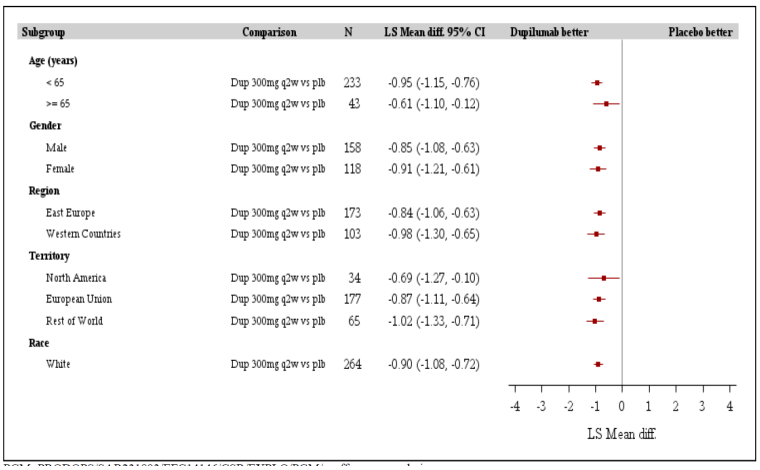


Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at Week 24 by demographic subgroups - ITT population

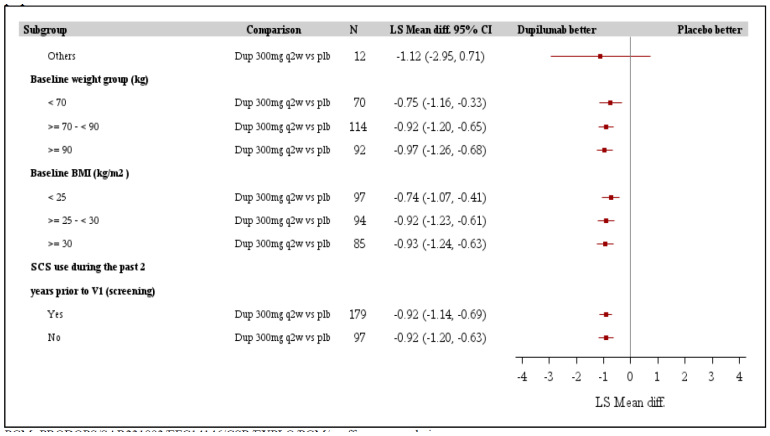
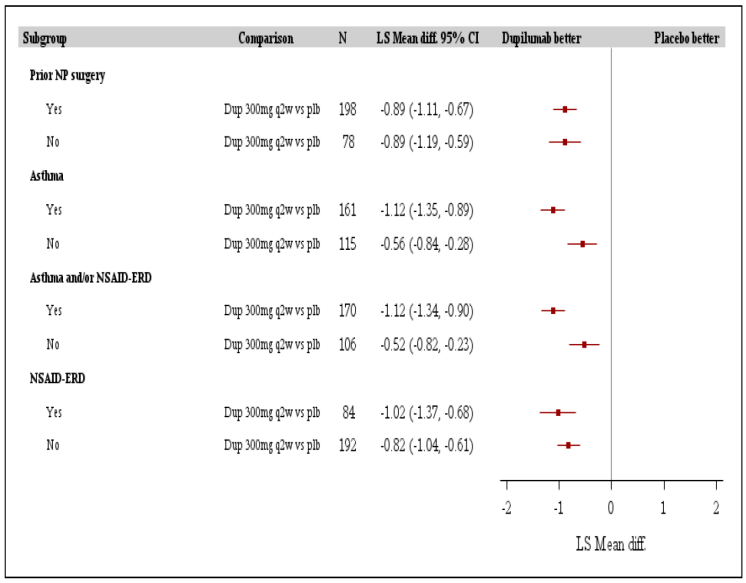


Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at Week 24 by disease characteristics subgroups - ITT population



Study EFC14280

- **Nasal polyps score (NPS) at Week 24- EFC14280**

Subgroup analyses by demographic characteristics were conducted on the mean change from baseline in NC score at Week 24. No qualitative interactions were observed and no meaningful treatment-by-subgroup quantitative interactions were observed based on age, gender, region, territory, race, ethnicity, weight, or SCS use in the prior 2 years

Subgroup analyses of the mean change from baseline at Week 24 in bilateral NPS based on disease characteristics at baseline showed no meaningful qualitative or quantitative treatment-by-subgroup interactions

A quantitative interaction ($p<0.05$) was detected with regard to the following subgroups:

- **age (nominal p = 0.0111)-** a magnitude of the treatment effect was greater in the subgroup of patients <65 years of age
- **ethnicity** (nominal p = 0.0151)- magnitude of the treatment effect was greater in the subgroup of patients who were not Hispanic or Latino
- **BMI (nominal p = 0.0297)**- magnitude of the treatment effect was greater in the patients with BMI <25 kg/m2 and ≥25 to <30 kg/m2 compared with patients with a BMI ≥30 kg/m2

Figure: Treatment effect on change from baseline in bilateral nasal polyps score (NPS) at Week 24 by demographic subgroups - ITT population- EFC14280

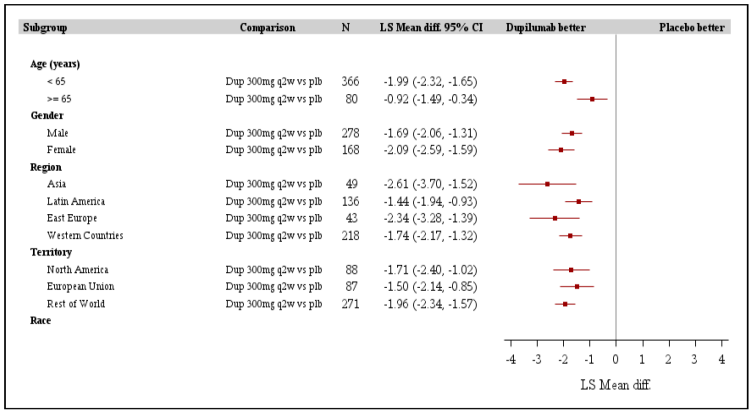


Figure: Treatment effect on change from baseline in bilateral NPS at Week 24 by demographic subgroups - ITT population- EFC14280

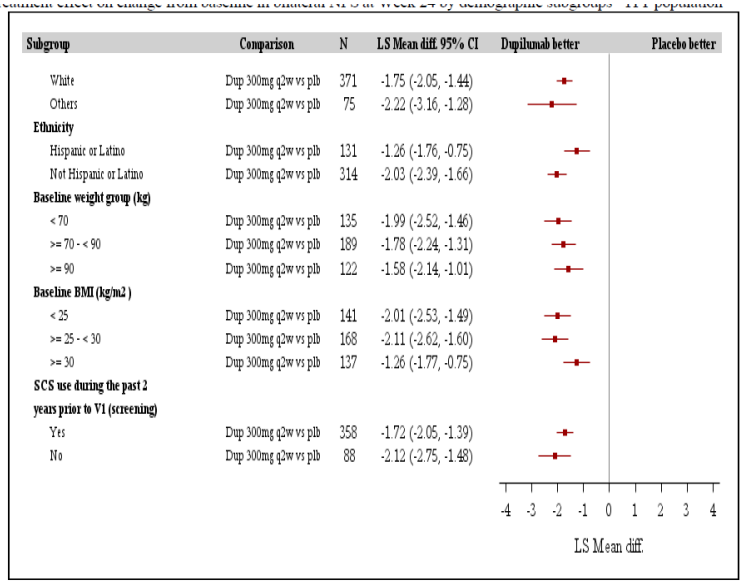
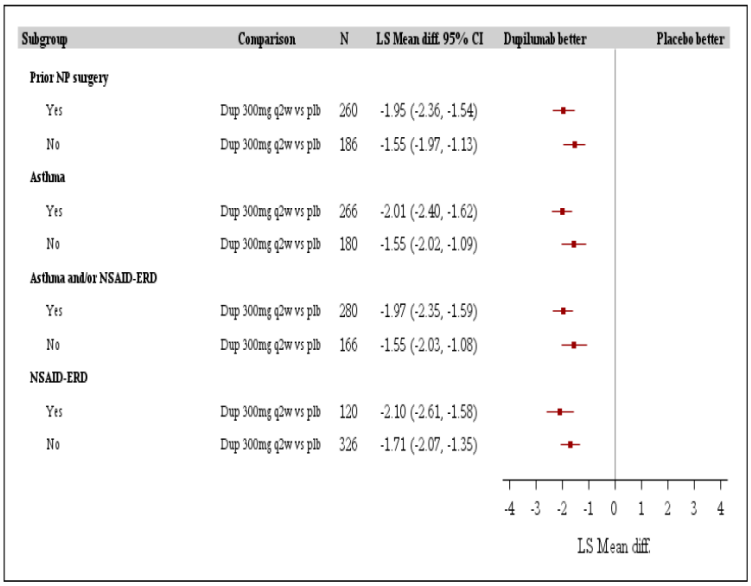


Figure: Treatment effect on change from baseline in bilateral nasal polyps score (NPS) at Week 24 by disease characteristics subgroups - ITT population- EFC14280



- **nasal congestion/obstruction at Week 24- EFC14280**

No qualitative interactions were observed and no meaningful treatment-by-subgroup quantitative interactions were observed based on age, gender, region, territory, race, ethnicity, weight, or SCS use in the prior 2 years.

Subgroup analyses of the mean change from baseline at Week 24 in NC score based on disease characteristics at baseline showed no qualitative interactions and no quantitative treatment-by subgroup interactions based on asthma history.

A quantitative interaction ($p<0.05$) was detected with regard to the following subgroups:

- **BMI (nominal p = 0.0374)-**a magnitude of the treatment effect was greater in the patients with BMI <25 kg/m2 compared with patients with a BMI and ≥25 to <30 kg/m2 and ≥30 kg/m2
- **history of prior NP surgery (nominal p=0.0161)** - a magnitude of the treatment effect was greater in the patients with prior surgery (LS mean difference versus placebo was -1.03) compared to patients without prior surgery (LS mean difference versus placebo was -0.64).
- **asthma and/or NSAID-ERD (nominal p=0.0402**)- a magnitude of the treatment effect was greater in the patients with asthma and/or NSAID-ERD compared to patients without asthma and/or **NSAID-ERD**
- **history of NSAID-ERD (nominal p=0.0060)-** a magnitude of the treatment effect was greater in the patients with NSAID-ERD compared to patients without NSAID-ERD

Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at

Week 24 by demographic subgroups - ITT population- EFC14280

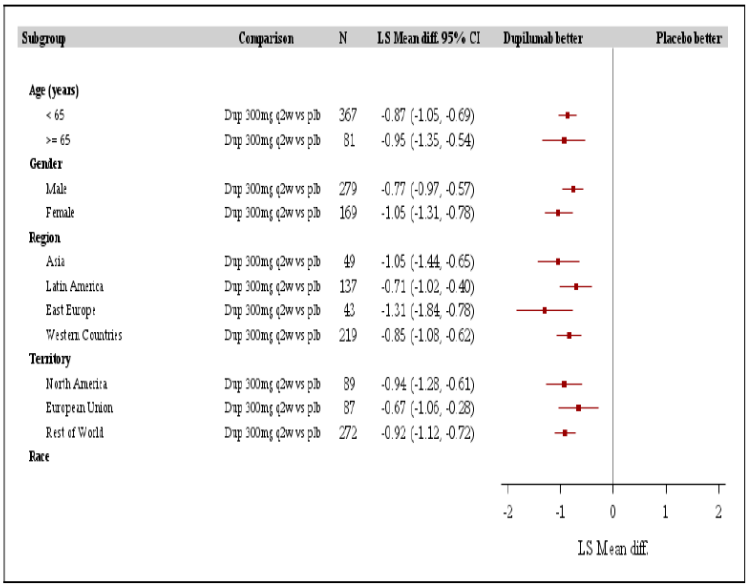


Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at Week 24 by demographic subgroups - ITT population- EFC14280

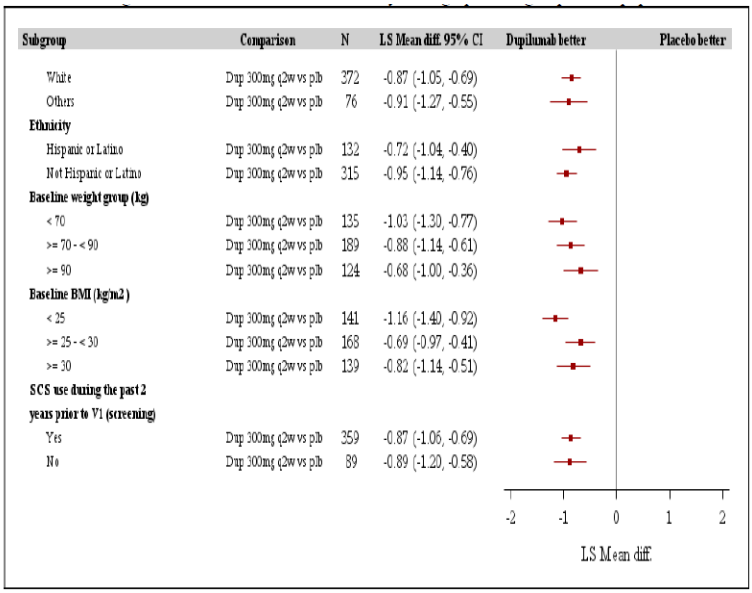


Figure: Treatment effect on change from baseline in nasal congestion/obstruction (NC) at Wee 24 by disease characteristics subgroups - ITT population-EFC14280

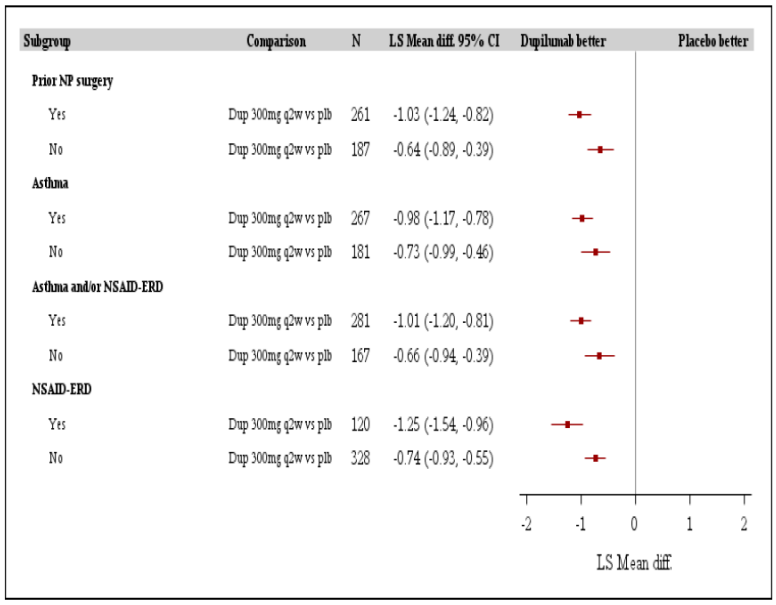
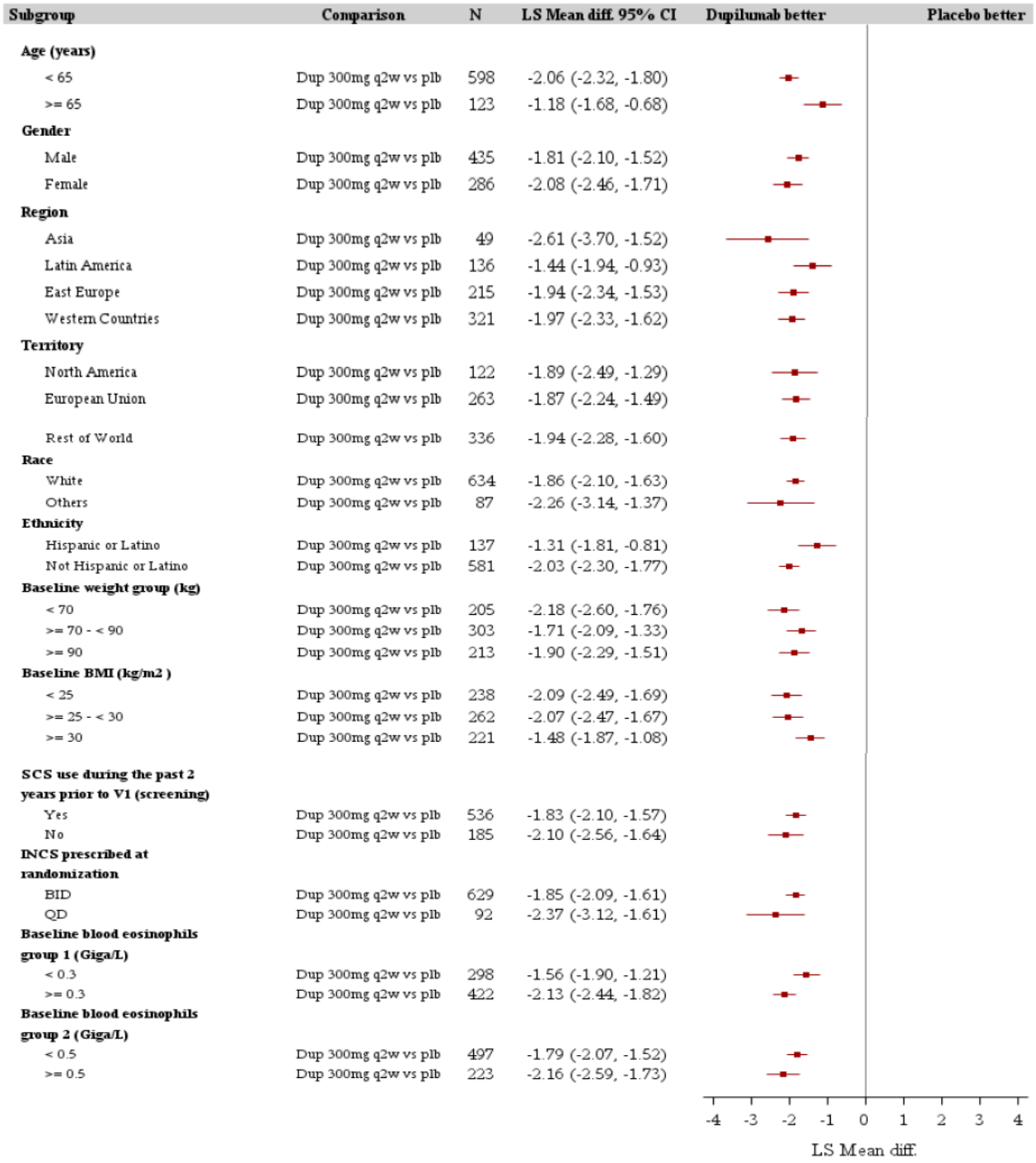
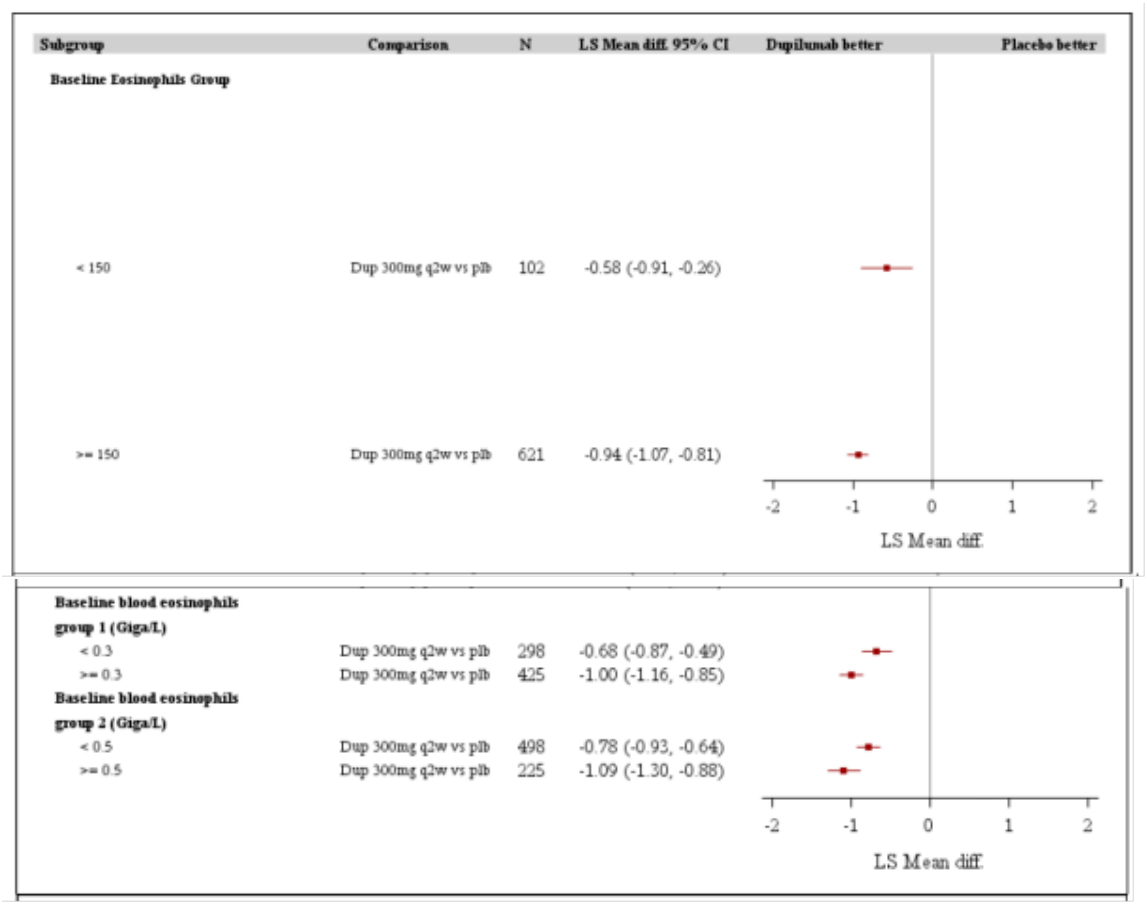


Figure: Forest plot for treatment effect on change from baseline in bilateral nasal polyps score (NPS) at Week 24 - pooled ITT population



There are no definitive or established biomarkers that can discern type 2 inflammation versus non-type 2 inflammation mediated CRSwNP. Due to the lack of the established biomarkers that predict response the Applicant has performed several subgroup analyses for NPS, LMK, and NC by eosinophil baseline level and other type 2 inflammatory biomarkers as requested by the Agency which confirmed that dupilumab was efficacious in patients across the baseline blood eosinophil subgroups (<0.15 versus ≥0.15 Giga/L) and baseline serum total IgE, periostin, and TARC subgroups (above or below median levels) (see below):

Forest plot for treatment effect on change from baseline in nasal congestion/obstruction (NC) at Week 24 - pooled ITT population



20% of patients were not receiving INCS at screening (Visit 1), all patients in the study underwent 4 weeks run-in period before randomization (V2) during which they received mometasone furoate nasal spray (MFNS, two actuations [50 µg/actuation] in each nostril BID). Thus all patients received at least 4 weeks of INCS at baseline prior to randomization. The change in baseline scores for NPS and nasal congestion/obstruction (NC) during the run-in (between Visit 1 and Visit 2) were minimal and similar between patients who were on INCS before screening and those who were INCS-naive at screening ie, 28 days before baseline and indicate that lack of INCS before screening (Visit A) doesn't affect disease severity at baseline (Visit 2). These data indicate a study population severe and uncontrolled by standard of care including INCS, SCS, and/or surgery.

EFC14280 and EFC14146: Disease severity at baseline for patients with or without prior INCS use - Randomized population

	EFC14280		EFC14146	
	All with prior INCS use (N=363)	All without prior INCS use (N=85)	All with prior INCS use (N=227)	All without prior INCS use (N=49)
NPS				
V1				
Number	344	81	213	46
Mean (SD)	6.34 (0.97)	6.51 (1.04)	6.04 (0.93)	6.26 (1.06)
Median	6.00	6.00	6.00	6.00
Q1 : Q3	5.50 : 7.00	6.00 : 7.50	5.50 : 6.50	5.50 : 7.00
Min : Max	4.5 : 8.0	4.5 : 8.0	4.5 : 8.0	4.5 : 8.0
V2				
Number	355	83	225	46
Mean (SD)	6.06 (1.19)	6.23 (1.34)	5.71 (1.28)	5.90 (1.28)
Median	6.00	6.00	6.00	6.00
Q1 : Q3	5.50 : 7.00	5.50 : 7.00	5.00 : 6.50	5.00 : 7.00
Min : Max	1.5 : 8.0	2.0 : 8.0	2.0 : 8.0	3.0 : 8.0
NC				
V1				
Number	342	79	215	43
Mean (SD)	2.59 (0.50)	2.62 (0.49)	2.47 (0.51)	2.63 (0.49)
Median	3.00	3.00	2.00	3.00
Q1 : Q3	2.00 : 3.00	2.00 : 3.00	2.00 : 3.00	2.00 : 3.00
Min : Max	1.0 : 3.0	2.0 : 3.0	1.0 : 3.0	2.0 : 3.0
V2				
Number	361	85	221	49
Mean (SD)	2.42 (0.68)	2.45 (0.59)	2.31 (0.64)	2.53 (0.58)
Median	3.00	2.00	2.00	3.00
Q1 : Q3	2.00 : 3.00	2.00 : 3.00	2.00 : 3.00	2.00 : 3.00
Min : Max	0.0 : 3.0	1.0 : 3.0	1.0 : 3.0	1.0 : 3.0

The Applicant has conducted an efficacy analysis of each subgroup as requested in the 1st RSI. The treatment effects are also summarized and were consistent and significant in all subgroups that had a sufficient number of subjects to allow statistical analysis Summary of LS mean changes from baseline at week 24.

c) Supportive study

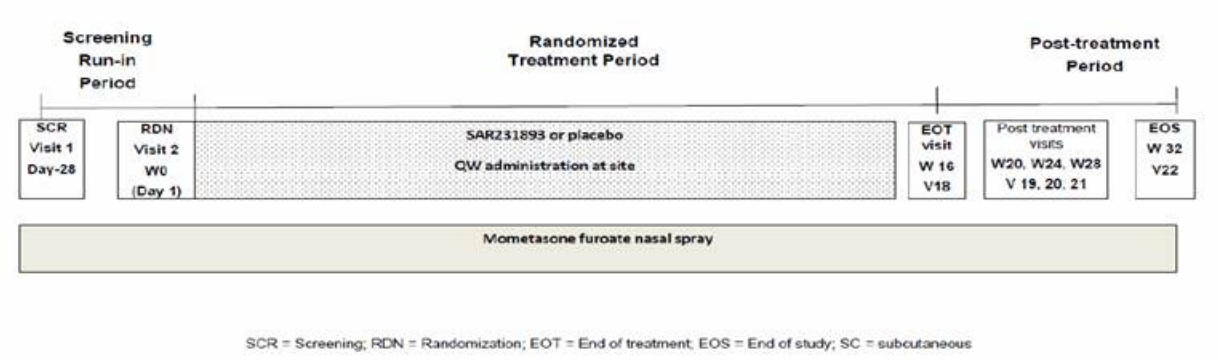
Study ACT12340

Title :
ACT12340: a Phase 2 proof of concept study evaluating the effect of dupilumab 300 mg administered subcutaneously (SC) once every week for 16 weeks, with a loading dose of 600 mg on Day 1, in patients with CRSwNP and chronic symptoms of sinusitis on a background therapy of mometasone furoate nasal spray (MFNS).

This study was a Phase 2 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the effect of 300 mg of dupilumab administered every week (QW) subcutaneous (SC) for 16 weeks with a loading dose of 600 milligrams (mg) on Day (D)1.

Methods

Study design



The clinical study consisted of three periods:

1. Screening run-in on mometasone fuorate nasal spray (MFNS) for 4 weeks
2. Randomized Dupilumab/Placebo Treatment Period (16 weeks)
3. Post-treatment Period for PK, immunogenicity, safety, and efficacy (16 weeks)

Patients were randomized using a 1:1 randomization ratio for dupilumab 300 mg qw and placebo.

Study participants

The population of ACT12340 was composed of patients >18 years of age with a physician endoscopic diagnosis of bilateral NP with a minimum bilateral NPS of 5 out of a maximum score of 8 for both nostrils despite completion of a prior topical intranasal corticosteroid (INCS) treatment for at least 8 weeks before screening and chronic symptoms of sinusitis. Excluded were patients who had undergone any nasal surgery (including polypectomy) within 6 months before screening or had more than 5 sino-nasal surgeries in the past, who required a burst of systemic corticosteroids within the 2 months before screening, were treated with monoclonal antibodies (mAB) or immunosuppressive treatment within 2 month before screening.

Treatments

The study treatments used were dupilumab or placebo. Sterile dupilumab and matching placebo was presented in 5 milliliter (mL) glass vials. Each vial contained a deliverable volume of 2 mL. The route and method of administration was SC by the Investigator or delegate.

At the first day of dosing, the patient received 2 injections as a loading dose of 600 mg. Thereafter, 300 mg QW was given as a single injection.

This study explored the 300 mg qw dose regimen. This dose was anticipated to saturate apparent target mediated clearance level (10-15 mg/L) and had been tested in two previous proof-of-concept studies performed with dupilumab in asthma and atopic dermatitis. The first dose employed a loading dose of 600 mg in order to achieve faster steady-state concentration. This loading dose range was supported by the acceptable safety profile of the highest loading dose (600 mg) demonstrated in the TDU12265 study.

Mometasone fuorate nasal spray was permitted as concomitant medication.

Objectives/Endpoints

The primary objective was to evaluate the efficacy of dupilumab in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score (NPS) in comparison to placebo.

The secondary objectives were to evaluate dupilumab in patients with bilateral nasal polyps, with regards to:

- Symptoms of sinusitis
- Computed Tomography (CT) scan changes
- Nasal Polyp Score in the sub-group of patients with comorbid asthma
- Safety and tolerability
- Pharmacodynamic responses based on suppression of Th-2 biomarkers
- Concentrations of dupilumab in serum
- Immune response to dupilumab (Anti-drug antibodies [ADA])

- Effect of dupilumab in patient reported outcomes (PROs) and quality of life (QoL) scales

The primary endpoint of the study was the change from baseline at Week 16 in bilateral endoscopic NPS.

Secondary endpoints were change from baseline at Week 16 in:

- Patient reported symptoms
  - 22-item Sinonasal Outcome Test (SNOT-22)
  - Subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and loss of sense of smell, (daily ante meridiem [AM] and post meridiem [PM] e-diary) month average
  - Number of nocturnal awakenings
  - Patient-rated rhinosinusitis symptoms severity using visual analog scale (VAS)
- Nasal peak inspiratory flow (NPIF)
- Smell test (University of Pennsylvania Smell Identification Test [UPSIT])
- The proportion of subjects demonstrating an improvement in NPS (defined as a reduction in bilateral polyp grade score of at least 1.0 from baseline at Week 16)
- Computed tomography scan assessments
- Time to first response (≥1 point improvement) in NPS.

The sample size estimation was based on the comparison between dupilumab 300 mg versus placebo with regard to the primary endpoint: change from baseline in NPS at Week 16.

Assuming a common standard deviation (SD) of 1.5, a 2-sided t-test and significance level of 0.05, 20% discontinuation rate, 28 patients per group will provide 80% power to detect a difference of 1.3 between dupilumab and placebo groups in the change of NPS from baseline to Week 16.

Randomization

Patients who meet the entry criteria were randomized via interactive voice response system (IVRS) using a 1:1 randomization ratio for dupilumab 300 mg QW or placebo QW for 16 weeks. The randomization was stratified based on asthma comorbidity status at visit 1 and nasal biopsy sampling (Yes or No) at visit 2. The study was double-blind to avoid the bias incurred by an unblinded design. The study was placebo-controlled to minimize bias and to present a control group to which differential efficacy and safety could be compared.

Participant flow

60 patients were randomized to receive either dupilumab 300 mg or matching placebo. In addition to the study treatment, all patients received an INCS. Of those 60 patients randomized, 53 completed the study period and 7 patients who were treated discontinued the study period prematurely. Study period discontinuation rates were higher in the placebo group compared to the dupilumab group with primary reasons being patient request (n=5 patients in the placebo group and 1 patient in the dupilumab group) and adverse event (n=4 patients in the placebo group).

Recruitment
Study Initiation Date (first patient enrolled): 27 August 2013
Study Completion Date (last patient completed): 05 November 2014

Baseline data
The mean age of patients enrolled in this study was 48.4 years (range: 25 to 64 years). More than half were males (56.7%) and all patients with the exception of 1 were White. The BMI of most

(n=46; 76.7%) patients was <30 kg/m2 with a mean BMI of 27.46 kg/m2 (range, 20.9 to 38 kg/m2). Over 73% of participants were from Europe, while the remainder was from the US. 43 (71.7%) out of 60 patients had at least 1 atopic medical history in the study with 40 patient's condition continuing post baseline. The most frequently reported history was allergic rhinitis (56.7%) reported by an equal number of patients in both treatment groups, followed by allergic conjunctivitis and hypersensitivity to NSAID (28.3% each).

All randomized patients reporting any rhinitis or sinusitis medical history within the past year prior to screening had their baseline conditions ongoing.

At baseline, the mean bilateral NPS was 5.77 out of a maximum of 8. The mean SNOT-22 score was 41 with a score range of 8 to 91 (maximum possible score of 110) and the UPSIT smell mean test result was 14.20. Upon CT-scan evaluation, most patients had complete opacification of the sinuses as assessed by the Lund-Mackay total mean score of 18.68.
Overall, mainly patients with moderate to severe NP disease were randomized in this study.

Most randomized patients (n=57; 95%) were taking INCS medications 2 months before screening. Three patients were not on a stable administration of MNFS prior to screening. Those medications included mometasone furoate (61.7%), fluticasone propionate (18.3%), and fluticasone furoate (11.7%) and were reported more frequently in the dupilumab group while beclometasone dipropionate and flucticasone (5% each) were reported more in the placebo group. Budesonide and triamcinolone acetonide were recorded for a single patient in each treatment group.

Sixty patients (30 patients in the placebo group and 30 patients in the dupilumab group) were randomized and included in the ITT group, which was the primary population for the efficacy parameters in this study. Of the 60 patients included in the safety population, all had at least 1 post treatment ADA sample and were available for the ADA population while those patients in the dupilumab group only (n=30) had at least 1 evaluable plasma concentration data and were considered in the PK population.

Outcomes and estimation

Primary endpoint

The primary endpoint was the **change from baseline at Week 16 in bilateral endoscopic NPS**.

Mean change from baseline at week 16 in bilateral endoscopic nasal polyps score- ITT population (MMRM)

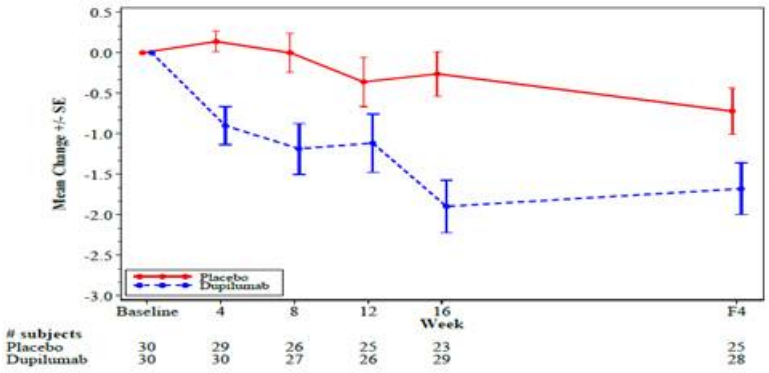
NPS	Placebo (N=30)	Dupilumab 300 mg qw (N=30)
Baseline		-
Number	30	30
Mean (SD)	5.67 (0.88)	5.87 (1.01)
Median	6.00	6.00
Min : Max	4.0 : 8.0	3.0 : 8.0
Week 16		
Number	23	29
Mean (SD)	5.39 (1.47)	3.97 (1.90)
Median	6.00	4.00
Min : Max	2.0 : 8.0	0.0 : 6.0
Change from baseline		
Number	23	29
Mean (SD)	-0.26 (1.32)	-1.90 (1.76)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-6.0 : 1.0
LS Mean (SE)[a]	-0.30 (0.34)	-1.85 (0.30)
LS Mean Diff, 95% CI[a]		-1.55 (-2.43, -0.67)
P-value vs placebo[a]		0.0009

CI=confidence interval; ITT=intent-to-treat; max=maximum; mg=milligram; min=minimum; MMRM=mixed-effect model with repeated measures; N=number; NPS=nasal polyp score; qw=every week (weekly); SD=standard deviation

[a]Analysis of a mixed model repeated measures (MMRM) model with treatment groups, stratification factor (asthma, biopsy), visit, treatment-by-visit interaction, baseline-by-visit interaction and baseline as covariates.

Baseline for NPS was the central reading at V2, in the event that there was missing data due to image quality, the central reading at V1 was used.

<u>Mean change from baseline in bilateral endoscopic nasal polyps score by visit- ITT population</u>



F4=follow up period 4

The results demonstrate improvement in the bilateral endoscopic NPS compared with placebo at Week 16 (p=0.0009). The LS mean change (SE) from baseline to Week 16 using MMRM analysis was -0.30 (0.34) for the placebo group and -1.85 (0.30) for the dupilumab group.

Subgroup analyses were performed on the mean change from baseline at Week 16 in bilateral NPS.

<u>Mean change from baseline at week 16 in bilateral endoscopic nasal polyps score by subgroup – ITT population</u>

	Placebo (N=30)	Dupilumab 300 mg qw (N=30)
Gender		
Male		
Number	12	18
Mean (SD)	-0.83 (1.34)	-1.72 (1.90)
Median	0.00	-2.00
Min : Max	-3.0 : 0.0	-6.0 : 1.0
Female		
Number	11	11
Mean (SD)	0.36 (1.03)	-2.18 (1.54)
Median	0.00	-2.00
Min : Max	-1.0 : 2.0	-4.0 : 0.0
Race		
Caucasian/White		
Number	23	28
Mean (SD)	-0.26 (1.32)	-1.82 (1.74)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-6.0 : 1.0
All other races		
Number	0	1
Mean (SD)		-4.00 (NC)
Median		-4.00
Min : Max		-4.0 : -4.0
Age group (year)		
>=18 and <45		
Number	6	10
Previous surgery for nasal polyposis (yes or no)		
Yes		
Number	14	16
Mean (SD)	-0.29 (1.33)	-2.56 (1.75)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-6.0 : 0.0
No		
Number	9	13
Mean (SD)	-0.22 (1.39)	-1.08 (1.44)
Median	0.00	-1.00
Min : Max	-3.0 : 2.0	-4.0 : 1.0
Mean (SD)	0.00 (1.10)	-1.60 (1.90)
Median	0.00	-0.50
Min : Max	-1.0 : 2.0	-4.0 : 0.0
>=45		
Number	17	19
Mean (SD)	-0.35 (1.41)	-2.05 (1.72)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-6.0 : 1.0
Baseline weight (kg)		
<90		
Number	15	21
Mean (SD)	-0.33 (1.29)	-1.71 (1.68)
Median	0.00	-1.00
Min : Max	-3.0 : 2.0	-4.0 : 1.0
>=90		
Number	8	8
Mean (SD)	-0.13 (1.46)	-2.38 (2.00)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-6.0 : 0.0
Baseline NPS		
<5		
Number	3	3
Mean (SD)	1.33 (1.15)	-2.33 (0.58)
Median	2.00	-2.00
Min : Max	0.0 : 2.0	-3.0 : -2.0
5 to 6		
Number	18	22
Mean (SD)	-0.56 (1.25)	-1.59 (1.71)
Median	0.00	-1.00
Min : Max	-3.0 : 1.0	-4.0 : 1.0
7 to 8		
Number	2	4
Mean (SD)	0.00 (0.00)	-3.25 (2.22)
Median	0.00	-3.00
Min : Max	0.0 : 0.0	-6.0 : -1.0

Co-morbid asthma		
Yes		
Number	15	15
Mean (SD)	0.27 (0.88)	-2.40 (2.03)
Median	0.00	-2.00
Min : Max	-1.0 : 2.0	-6.0 : 1.0
No		
Number	8	14
Mean (SD)	-1.25 (1.49)	-1.36 (1.28)
Median	-0.50	-1.50
Min : Max	-3.0 : 0.0	-4.0 : 0.0
Region		
Europe		
Number	19	19
Mean (SD)	-0.32 (1.42)	-1.58 (1.64)
Median	0.00	-2.00
Min : Max	-3.0 : 2.0	-4.0 : 1.0
US		
Number	4	10
Mean (SD)	0.00 (0.82)	-2.50 (1.90)
Median	0.00	-2.00
Min : Max	-1.0 : 1.0	-6.0 : 0.0

ITT=intent-to-treat; max=maximum; mg=milligram; min=minimum; kg=kilogram; N=number; NPS=nasal polyp score; qw=every week (weekly); SD=standard deviation; US=United States

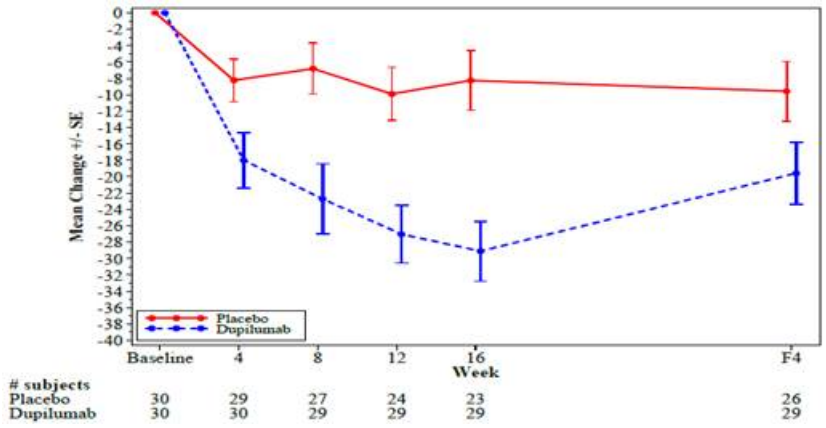
Mean decreases in NPS at Week 16 in the comorbid asthma group was consistent with results seen in the overall population where dupilumab demonstrated a statistically significant mean improvement (LS mean difference of -2.30 [95% CI: -3.41, -1.18] p=0.0002). Baseline weight <90 kg and ≥ 90 kg did not affect the treatment benefit of dupilumab.

Secondary endpoints

The change from baseline at Week 16 in SNOT-22

An improvement in favour of dupilumab was seen. The LS mean change (SE) from baseline at Week 16 was -9.17 (2.96) in the placebo group and -27.28 (2.71) in the dupilumab group, resulting in a LS mean difference of -18.11 (95% CI: -25.62, -10.60, p<0.0001).

Mean change from baseline in SNOT-22 total score- ITT population



Change from baseline at Week 16 in subject assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and loss of sense of smell, (daily AM and PM e-diary) month average

Nasal congestion/obstruction

The dupilumab group showed greater improvement at Week 16 in PM and AM symptom score compared to placebo. Statistical significance in favor of dupilumab was observed in the difference between groups in the change from baseline at Week 16 in subject assessed PM symptom score for nasal congestion/obstruction (LS mean difference of -0.71 [95% CI: -1.05, -0.37]; p=0.0001). The

mean change from baseline at Week 16 in AM symptoms for congestion/obstruction was in favour of dupilumab with a LS mean difference of -0.69 (95% CI: -1.05, -0.33); p=0.0003.
At the end of the 16 week follow up period, improvement compared to baseline was sustained in both treatment groups for PM and AM symptoms.

2.4.3. Discussion on clinical efficacy

The MAH submitted a variation application for the following indications:

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

No formal dose response study was performed in patients with nasal polyps. The dose regimens were selected based on the totality of clinical evidence in the dupilumab program including data from Phase 2 efficacy and safety study (ACT12340) in patients with nasal polyps and symptoms of chronic sinusitis, the result of Phase 2b dose ranging study in patients with moderate to severe asthma (DRI12544), the Phase 2b dose ranging study (R668-AD-1021) and phase 3 studies (R668-AD-1334 and R668-AD-1416) in patients with moderate to severe atopic dermatitis (AD), as well as the supportive PK/pharmacodynamic [PD] analysis.

It is noted that the proposed dosing regimen and doses tested in pivotal studies deviates from the one that was tested in the proof of concept study ACT12340 (i.e. q2w instead of weekly dosing; no loading dose). The simulated concentration-time profiles for dupilumab in typical NP patients receiving 300 mg q2w with or without a loading dose of 600 mg (-please see discussion in the PK section) confirmed that the absence of loading dose results in longer time to steady state, but does not impact the steady state level. While it is acknowledged that the PK steady state would take slightly longer without a loading dose, the time-course as well as extent of response over the 24 to 52-week period in the phase 3 studies is similar with or without a loading dose, this supports the Applicant's choice to not include a loading dose for the CRSwNP program.

The applicant provided a justification for q2w regimen. The SNOT-22 results from 300mg q2w being used in asthma patients with NP as co-morbidity were discussed and used as a justification for the selected dose. In asthma dose ranging study (DRI12544), 300 mg q2w regimen demonstrated a robust treatment effect across all relevant indices of drug action, while lower dose or less frequent regimens 200 mg q2w and 300mg q4w showed less effect in some endpoints including SNOT-22.

In both studies, dupilumab significantly improved the sense of smell with improvement noted as early as Week 2. Nearly two-thirds of the dupilumab-treated patients who were anosmic at baseline (UPSIT score ≤18) improved their UPSIT score to the non-anosmic range of >19 at Week 24. In the placebo group almost all anosmic patients at baseline remained anosmic.

Design and conduct of clinical studies

The applicant performed two pivotal studies in support this variation application.

Study EFC14146 was a randomized, double-blind, placebo-controlled, parallel group phase III study. The study consisted of 3 periods a run-in period of 4 weeks, a treatment period of 24 weeks and a post treatment period of 24 weeks.

In total 276 patients with CRSwNP were randomized 1:1 to Dupilumab 300 mg q2w or Placebo. The patient population consisted of patients 18 years and older with high CRSwNP disease burden

(based on polyps score) and symptoms of NC and loss of smell or rhinorrhea for at least 12 weeks prior to randomization (8 weeks prior to screening) despite therapy with intranasal corticosteroids, systemic corticosteroids in the past 2 years or sino-nasal surgery. The demographic and baseline characteristics were generally similar between treatment groups in the randomized population. Chronic rhinosinusitis with nasal polyps (CRSwNP) history was comparable among the treatment groups as well as the disease baseline characteristics.

Mometasone furoate (NASONEX) as background medication was to be administered by the patients in each nostril twice daily.

Two co-primary endpoints, change from baseline to week 24 in NPS and change from baseline to week 24 in NC, were planned with the protocol.

Furthermore, six key secondary endpoints were planned to be tested in hierarchical order in order to account for multiplicity: 1) change from baseline in LMK score at week 24, 2) change from baseline in TSS at week 24, 3) change from baseline in UPSIT at week 24, 4) change from baseline in loss of smell daily symptoms at week 24, 5) change from baseline in SNOT-22 at week 24,

Study EFC14280 was a randomized, double-blind, placebo-controlled, parallel arm phase III study. The study consisted of a run-in period of 4 weeks, a randomized treatment period of 52 weeks, where patients in Arm B were switched to dupilumab q4w dosing regimen at week 24 and a posttreatment period of 12 weeks.

In total 448 subjects were randomized 1:1:1 to Dupilumab 300 mg q2w (arm A), Dupilumab 300 mg q2w/q4w (arm B) or Placebo (arm C). The patient population consisted of patients 18 years and older with high CRSwNP disease burden (based on polyps score) and symptoms of NC and loss of smell or rhinorrhea for at least 12 weeks prior to randomization (8 weeks prior to screening) despite therapy with intranasal corticosteroids, systemic corticosteroids in the past 2 years or sino-nasal surgery. The demographic and baseline characteristics were generally similar between treatment groups in the randomized population. Chronic rhinosinusitis with nasal polyps (CRSwNP) history was comparable among the treatment groups as well as the disease baseline characteristics.

Mometasone furoate (NASONEX) as background medication was to be administered by the patients in each nostril twice daily.

Two co-primary endpoints, change from baseline to week 24 in NPS and change from baseline to week 24 in NC, were planned with the protocol (pooled arms A+B vs. C).

Furthermore, six key secondary endpoints were planned to be tested in hierarchical order in order to account for multiplicity: 1) change from baseline in LMK score at week 24 (pooled arms A+B vs. C), 2)change from baseline in TSS at week 24 (pooled arms A+B vs. C), 3) change from baseline in UPSIT at week 24 (pooled arms A+B vs. C), 4) change from baseline in loss of smell daily symptoms at week 24 (pooled arms A+B vs. C), 5) change from baseline in SNOT-22 at week 24 (pooled arms A+B vs. C), , 6)proportion of patients with SCS rescue or surgery for NP during the treatment period, 7) change from baseline in NPS at week 52 (A vs. C), 8) change from baseline in NC at week 52 (A vs. C), 9) change from baseline in NPS at week 52 (B vs. C), and 10) change from baseline in NC at week 52 (B vs. C).

All enrolled patients required to receive prior treatment with SCS or be intolerant to SCS or underwent surgery for NP.

Similar protocol amendments and changes in the planned analyses were made in both studies. These changes were unlikely to have a significant impact on the study results. In both studies a number of patients had a deviation considered critical or major (Study EFC14146: 29.4% of patients in the dupilumab group and 42.9% of patients in the placebo group, Study EFC14280:

38.7% of patients in the dupilumab 300 mg q2w group, 40.7% of patients in the 300 mg q2w-q4w group, and 49.7% of patients in the placebo group).

There were 2 co-primary endpoints e.g nasal polyposis score (NPS) at week 24 and nasal congestion/obstruction score (NCS) at week 24. This approach is acceptable as change in nasal polyp size on its own is not considered sufficient as the primary endpoint as the interpretation of the clinical relevance of a reduction is difficult (as no MCID has been established) and therefore, adding an endpoint evaluating the impact of symptoms is of key importance in measuring outcomes in nasal polyposis.

Efficacy data and additional analyses

In study EFC14146, the mean age of the randomized population was 50.49 (range from 22 to 85 years), over half of the patients (158 [57.2%]) were males and the majority of patients were white (95.7%).161 randomized patients (58.3%) had a history of asthma whereas a total of 30.4% had a history of NSAID-ERD.

In study EFC14280, the mean age of the randomized population was 51.95 years with a range of 18 to 83 years. Approximately two-thirds (62.3%) of patients were males; and the majority (83.0%) of patients were White. 59.6% of randomized patients had a history of asthma and 26.8% had a history of NSAID-ERD.

Overall, the literature suggests that CRSwNP increases with age, with a mean onset across all ethnic groups of 42 years. NP is uncommon under the age of 20 years and occurs more frequently in men than in women; aspirin-sensitive patients, however, are more likely to be women.

The population which was recruited to both pivotal studies seems to reflect this literature finding.

In both pivotal studies the majority of patients had increased baseline blood eosinophils level. In study EFC14146, at baseline, 87.3% of patients had blood eosinophils ≥0.15 Giga/L and 59.1% of patients had blood eosinophils ≥0.3 Giga/L. In study EFC14280, at baseline 85 % of patients had blood eosinophils and ≥0.15 and 58.6% of patients had blood eosinophils ≥0.3 Giga/L.

It is noted that about 20% of patients in both studies did not report receiving any intranasal corticosteroid medications in the year before screening.

In general, it can be concluded that not all patients were receiving the maximum treatment with intranasal corticosteroid prior to enrolment and in fact some patients were not receiving any treatment. It can be agreed that the lack of INCS before screening did not affect significantly disease severity at baseline and the response to mometasone furoate during the run-in period was small in all patients.

Most randomized patients (>80%) in both pivotal studies were taking intranasal corticosteroid medications in the year before screening. The most commonly used prior intranasal corticosteroid medications included mometasone furoate/mometasone (45.3% and 6.5% in study EFC14146 and 33.5% and 33.5% in study EFC14280). In this study, other types of intranasal corticosteroid medications were used less frequently and doses varied.

Overall 97.4% of randomized patients had a history of prior sino-nasal surgery and/or SCS use during the past 2 years, indicating inadequate control after maximal medical/surgical treatment. In study EFC14146, a total of 71.7% patients had previous surgery for NP and in the 2 years prior to randomization, 64.9% of patients received SCS at least once. In a second pivotal study, less patients underwent previous NP surgery (58.3%) whereas more patients had received treatments with SCS within 2 years prior to randomisation (80.1%).

The Applicant described the enrolled patient population as severe as they had failed second line therapy (e.g. surgery for NP or treatment with SCS), and presented with objective measures (mean NPS of 5.97/8 - sinus opacification measured by CT-scan ad LMK consistent with extensive disease) considered severe. However, if only symptoms are considered, the enrolled patient population was within moderate to severe disease category at baseline.

It is well accepted that for CRSwNP, the severity of disease should be primarily based on assessment of symptoms rather than polyp size. The mean nasal congestion score of 2.4 out of maximum score of 3 (2=moderate, 3=severe); mean loss of smell at baseline of 2.74 out of a maximum score of 3; mean UPSIT score of 13.98 (range of 0 to 40 with a score $\leq$18 indicating anosmia) and a mean daily total symptom score (TSS- a composite symptom score of nasal congestion/obstruction, rhinorrhea and sense of smell) of 7.16 out of maximum score of 9 were all indicative of a disease status in the severe spectrum.

The 22-Item Sino-nasal Outcome Test (SNOT22) was >50, means values 49.40 (in study EFC14146) and 51.86 (in EFC14280) (moderate >20-50 and severe as >50, Toma S1, Hopkins C2.). In addition, the mean VAS of the trial population was 7.88 above the treshold of 7 referred to in the European Position paper on Rhinisinusitis and Nasal Polyps (EPOS 2012). Based on the totality of the baseline mean scores and severity distribution across signs and symptoms of disease, the Applicant considers that the vast majority of the phase 3 population is consistent with a severe and uncontrolled setting of CRSwNP.

Study EFC14146

Of the 276 patients randomized, 263 patients completed 24 weeks of study treatment. The demographic and baseline characteristics were generally similar between dupilumab and placebo groups.

Statistical significance was reached for the 2 co-primary efficacy endpoints (change from baseline in NPS and change from baseline in NC at Week 24) and all multiplicity adjusted key secondary endpoints including sinus opacification as measured by CT scan LMK score.

The dupilumab 300 mg q2w regimen demonstrated clinically meaningful mean improvement in the bilateral endoscopic NPS and NC compared with placebo at Week 24 (co-primary endpoints). The LS mean change in NPS from baseline to Week 24 was -1.89 for the 300 mg q2w dupilumab group and 0.17 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -2.06 with 95% CI: -2.43 to -1.69 (p <0.0001). The improvement in NPS was observed early at week 8 (first post-baseline assessment) and showed continuous improvement through week 24. The LS mean change in NC score from baseline to Week 24 was -1.34 for the dupilumab group and -0.45 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -0.89 with 95% CI: -1.07 to -0.71 (p <0.0001). The onset of difference was observed as early as the first post-baseline monthly average score at Week 4. Similar to NPS, the NC showed continued improvement through Week 24. The sensitivity analyses conducted showed similar results and supported the robustness of the results. The subgroup analyses of the primary endpoints demonstrated consistent results across the demographic and baseline characteristics.

Results from the key secondary endpoints were consistent with the results from the primary endpoints. The LS mean change in sinus opacification as measured by CT scan LMK from baseline to Week 24 was -8.18 for the dupilumab group and -0.74 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -7.44 with 95% CI: -8.35 to -6.53 (p <0.0001). The LS mean change in total symptom score from baseline to Week 24 was -3.77 for the dupilumab group and -1.17 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -2.61 with 95% CI: -3.04 to -2.17 (p <0.0001).

Other key secondary efficacy endpoints, included loss of sense of smell (individual daily loss of smell severity item of symptoms e-diary score and UPSIT score), the most troublesome symptom complaint by CRSwNP patients and generally refractory to currently available therapy, and disease specific HRQoL (SNOT-22 total score) at Week 24. Similar to the primary and key secondary endpoints dupilumab demonstrated clinically meaningful improvements in these endpoints. LS mean difference in UPSIT score in the dupilumab group versus placebo was 10.56 with 95% CI: 8.79 to 12.34 (p <0.0001). The LS mean difference in loss of smell score in the dupilumab group versus placebo was -1.12 with 95% CI: -1.31 to -0.93 (p <0.0001). The LS mean difference in SNOT-22 total score in the dupilumab group versus placebo was -21.12 with 95% CI: -25.17 to -17.06 (p <0.0001).

At week 24 dupilumab treatment was discontinued. In the following 24-week follow-up period the treatment effect diminished without rebound across all endpoints. At Week 48, the LS mean difference in NPS score in the dupilumab group versus placebo was reduced to -0.80 with 95% CI: -1.11 to -0.48 and the LS mean difference in NC in the dupilumab group versus placebo was -0.26 with 95% CI: -0.46 to -0.06.

Fifty-eight point three percent (58.3%) of the CRSwNP patients had asthma and 30.4% had a history of NSAID-ERD. In CRSwNP patients with asthma, dupilumab 300 mg q2w demonstrated clinically meaningful improvements in mean NPS, NC, sinus opacification as measured by CT scan LMK score, SNOT-22 total score, FEV1 and ACQ-6 compared with placebo at Week 24.

Study EFC14280

Of the 448 patients randomized, 418 patients completed the first 24 weeks of study treatment. Twenty nine (29) patients discontinued from the study treatment prior to Week 24 (12.4% in placebo versus 3.4% in the dupilumab group) and 1 patient did not receive any study treatment. The demographic and baseline characteristics were generally similar between treatment groups in the randomized population.

Statistical significance was reached for the 2 co-primary efficacy endpoints and all multiplicity adjusted key secondary endpoints.

At week 24 Dupilumab at 300 mg q2w demonstrated a statistically and clinically meaningful improvement in the bilateral endoscopic NPS and NC symptom score compared with placebo. The LS mean change in NPS from baseline to Week 24 was -1.71 for the 300 mg q2w dupilumab group (pooled Arm A+B) and was +0.10 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -1.80 with 95% CI: -2.10 to -1.51 (p <0.0001). The LS mean change in NC score from baseline to Week 24 was -1.25 for the 300 mg q2w dupilumab group (pooled Arm A+B) and was -0.38 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -0.87 with 95% CI: -1.03 to -0.71 (p <0.0001). A rapid onset of efficacy was seen and differences between the dupilumab groups and placebo were seen as early as week 4 post-baseline. The improvements continued through week 24. The results of the sensitivity analyses performed (including as-observed analysis taking into account all data in patients who receive SCS for any reason or missing data) were similar and support the results from the primary analysis. Subgroup analyses show consisted results across demographic and baseline characteristics. The onset of effect for dupilumab was rapid, with a meaningful difference between the dupilumab groups and placebo group observed as early as the first assessment for each endpoint (Week 2 to Week 4) after initiation of treatment.

Results from the key secondary endpoints were consistent with the results from the primary endpoints. The LS mean change in sinus opacification as measured by CT scan LMK score from baseline to Week 24 was -5.21 for the 300 mg q2w dupilumab group (pooled Arm A+B) and was -0.09 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -

5.13 with 95% CI: -5.80 to -4.46 (p <0.0001). The LS mean change in total symptom score from baseline to Week 24 was -3.45 for the 300 mg q2w dupilumab group (pooled Arm A+B) and was -1.00 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -2.44 with 95% CI: -2.87 to -2.02 (p <0.0001). The LS mean difference in UPSIT score in the dupilumab 300 mg q2w group (pooled Arm A+B) versus placebo was 10.52 with 95% CI: 8.98 to 12.07 (p <0.0001). The LS mean difference in loss of smell score in the dupilumab 300 mg q2w group (pooled Arm A+B) versus placebo was -0.98 with 95% CI: -1.15 to -0.81 (p <0.0001). The LS mean difference in SNOT-22 total score in the dupilumab 300 mg q2w group (pooled Arm A+B) versus placebo was -17.36 with 95% CI: -20.87 to -13.85 (p <0.0001).

Through week 52 patients in both dupilumab Arm A (continued on 300 mg q2w) and Arm B (switched to 300 mg q4w at Week 24) showed continued improvement without reaching a plateau for nearly all endpoints, with the exception of UPSIT for which a plateau in the treatment effect was observed between Weeks 24 and 52. The LS mean difference in NPS in the 300 mg q2w dupilumab group (Arm A) versus placebo at Week 52 was -2.40 with 95% CI: -2.77 to -2.02 (p <0.0001). Similarly, the LS mean difference in the 300 mg q2w-q4w dupilumab group (Arm B) versus placebo at Week 52 was -2.21 with 95% CI: -2.59 to -1.83 (nominal p <0.0001). With regards to most clinical endpoints, the results of the two dosing regimens were similar. The observed improvement between Weeks 24 and 52 in NPS and LMK was numerically greater in the patients who continued on the q2w regimen compared with those who switched to q4w dosing.

The dupilumab drug concentration data showed that more patients in the 300 mg q2wq4w regimen (8.7%) had steady-state concentrations that were below the limit of quantitation (0.078 mg/L) than those in the 300 mg q2w regimen (1.8%) at Week 52. A lower proportion of patients at the 300 mg q2w-q4w regimen (86%) maintained steady-state trough concentrations above the EC50 (1.75 mg/L) of NPS response compared to 300 mg q2w (97%). The proportion of patients who maintained Week 52 steady-state trough concentrations above the EC90 (15.8 mg/L) of NPS response was 98%, and 41% at 300 mg q2w and 300 mg q2w-q4w regimens, respectively.

In addition, treatment-emergent adverse events (TEAEs) of sinusitis, nasal polyps, and asthma which are generally associated with worsening of CRSwNP or asthma, were numerically higher in patients who switched at Week 24 from dupilumab 300 mg q2w to q4w dosing compared with those who remained on q2w. This suggests that the q4w arm may have suboptimal disease control in a subset of patients and the imbalance noted in TEAEs was indicative of gradual loss of clinical symptom control for both CRSwNP and comorbid asthma.

The number of patients who underwent surgery for NP and also received treatment with SCS was 106 patients (38.4%) in EFC14146, and 186 patients (41.5%) in EFC14280. The number of patients who underwent surgery for NP but were not treated with SCS was 92 (33.3%) in EFC14146 and 75 patients (16.7%) in EFC14280. The efficacy in these subgroups was consistent with the overall efficacy in the ITT. The number of patients who received treatment with SCS only was 73 (26.4%) in EFC14146 and 173 (38.6%) in EFC14280. Only 5 patients (3 placebo and 2 dupilumab) in EFC14146 and 14 patients (5 placebo and 9 dupilumab) in EFC14280 had not undergone prior surgery or previously received treatment with SCS. Although the small numbers by subgroup does not allow any statistical comparison between treatment groups, reduction in NPS and NC in this subgroup was consistent with the overall efficacy in the ITT.

In the phase 3 studies in CRSwNP there was a limited number of patients ≥110 kg. Of the 276 patients randomized in study EFC14146, 19 (11 placebo and 8 dupilumab patients) were ≥110 kg. In EFC14280, 23 out of 448 patients (7 placebo and 16 dupilumab patients) were ≥110 kg. Only 4 patients (3 placebo and 1 dupilumab) in EFC14146 study and 7 patients (2 placebo and 5 dupilumab) in EFC14280 study were ≥130 kg. Despite the limited sample size the magnitude of the effect in this subgroup was consistent with the overall observations in the ITT.In relation to nasal

polyposis score (NPS) at week 24, in both pivotal studies statistically significant improvement was observed in the dupilumab groups (in arm A in study EFC14146 and pooled arm A + B in study EFC14280) with slightly better results reported in study EFC14146.

In study EFC14146, an LS mean change from baseline to Week 24 was -1.89 for the 300 mg q2w dupilumab group and +0.17 for the placebo group (LS mean difference versus placebo: -2.06 with 95% CI: -2.43 to -1.69 ($p<0.0001$).

The applicant provided Responder Analysis at Week 24 e.g the percentage of patients with a change from baseline in bilateral endoscopic NPS ≥1 point or ≥2 points at Week 24.

In relation to change from baseline in nasal congestion/obstruction score (NCS) at Week 24, again for both pivotal studies statistically significant improvement was observed in the dupilumab groups (in arm A in study EFC14146 and in pooled arm A + B in study EFC14280).

In study EFC14146, an LS mean change from baseline to Week 24 was -1.34 for the dupilumab group and -0.45 for the placebo group (LS mean difference versus placebo: -0.89 with 95% CI: -1.07 to -0.71; $p<0.0001$).

The results of secondary endpoints were consistent with the results the primary endpoints showing significant treatment effects in patients receiving Dupilumab as compared to patients receiving placebo.

Supportive study ACT12340

ACT12340 was a proof of concept study in which the effect of 300 mg of dupilumab administered qw SC (with 600 mg loading dose) for 16 weeks was compared to placebo.

The study population included patients with nasal polyps with a minimum bilateral NPS of 5 out of a maximum score of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening. In addition, enrolled patients had to report at least two of symptoms such as nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell.

In contrast to the pivotal studies, in study ACT12340 there was no requirement for minimal nasal congestion score at baseline or having history of prior treatment with SCS or surgery for NP.

Sixty (60) patients were randomized and 23 completed this study in the placebo arm and 28 in the treatment arm.

Despite these differences in the in the inclusion criteria, the enrolled study population was only slightly less severe as compared to patients enrolled to the pivotal studies (the mean bilateral NPS was 5.77, the mean SNOT-22 score was 41, Lund-Mackay total mean score of 18.68).

The primary efficacy endpoint was the change from baseline at Week 16 in bilateral endoscopic NPS which is acceptable in the context of a proof of concept study. At Week 16 a significant improvement in bilateral endoscopic NPS was reported in the Dupilumab arm as compared to the placebo arm (LS mean difference was -1.55). The reported treatment effect was similar to the effect reported in pivotal studies for this endpoint (In study EFC14146, LS mean difference versus placebo was -2.06, in study EFC14280, LS mean difference versus placebo was -1.80)

The results of secondary endpoints supported the primary efficacy endpoint results.

The proposed indication was as follows:
Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on maintenance treatment in adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) who previously failed or are intolerant or contraindicated to systemic corticosteroids and/or surgery.

Dupixent is indicated to reduce the need for surgery and systemic corticosteroid use in adult patients with inadequately controlled severe CRSwNP.

The second part of the indication was considered not acceptable by the CHMP as he data provided do not support an indication in reducing the need for surgery and systemic corticosteroid use . Reduction of need for surgery and use of CS are not considered as an indication as such. Indeed, As per the SmPC guideline, section 4.1 of the SmPC should define:
- the target disease or condition, distinguishing between treatment, prevention and diagnostic indication;
- when appropriate, the target population(s), especially when restrictions to the patient population(s) apply (including age groups and, when relevant, particular genotype);
- any mandatory conditions of product usage not covered more appropriately in other parts of the SmPC, when relevant.
Furthermore, study endpoints should not be presented in indications. This part of the indication was therefore dropped by the applicant…]

However it was considered by CHMP that some information would be important to provide to prescribers. Therefore results related to reduction of surgery and reduction of systemic corticosteroid use are included in section 5.1.

The CHMP also considered that the word "*maintenance"* should be removed from the indication. Information about long term use is included in Section 4.2 of the SmPC.

Additionally the CHMP considered that the population defined in the proposed indication was too broad and that the patient population for which dupixent should be used should be patients for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

In conclusion, the agreed indication is:

Dupixent is indicated as an add-on therapy with intrasanal corticosteroids for the treatment in adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) in patients for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Paediatric patients

The applicant proposed to add the following information to the SmPC: *The safety and efficacy of dupilumab in children with atopic dermatitis below the age of 12 years have not been established (see section 5.2). No data are available. CRSwNP does not normally occur in children. The safety and efficacy in children with CRSwNP below the age of 18 years have not been established (see section 5.2). No data are available*. The proposed wording is acceptable.

Elderly patients (≥65 years)

The applicant proposed to add the following information to the SmPC: *No dose adjustment is recommended for elderly patients (see section 5.1).* In the subgroup analysis Age group (<65, ≥65 years) no differences in the efficacy were seen. The proposed wording is acceptable

Body weight

The applicant proposed to add the following information to the SmPC: *No dose adjustment for body weight is recommended in adults with atopic dermatitis or CRSwNP (see section 5.2). In the subgroup analysis baseline weight (<70, ≥70- < 90, ≥ 90 kg; <60, ≥ 60 kg)* no differences in the efficacy were seen. However, considering that exposure is significantly associated with the body weight (e.g at the proposed dose of 300 mg q2w, exposures were ~60% higher and ~35% lower in patients weighing 53 kg and 110 kg, respectively, compared to a typical 79 kg patient) further discussion on the efficacy results was requested in patients with very high body weight. In conclusion, the effect of body weight on exposure is not considered to be clinically important. The absence of a dosing recommendation in the SmPC with regard to body weight was therefore considered justified. Updated information is provided in section 5.2 of the SmPC to reflect the limited information.

2.4.4. Conclusions on the clinical efficacy

The efficacy results from the pivotal Phase 3 studies (EFC14146 and EFC14280) demonstrated that the 300 mg q2w dose regimen provided statistically significant improvements in NPS and NC at both Week 24 (EFC14146 and EFC14280) and at Week 52 (EFC14280) compared to placebo, in adult patients with CRSwNP who were inadequately controlled with intranasal corticosteroids.

Based on the improvements seen in the primary and secondary endpoints of the pivotal studies, it is agreed that dupilumab is effective in the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP).

The agreed posology is an initial dose of 300 mg followed by 300 mg given every other week.

2.5. Clinical safety

Introduction

Duplilumab is approved in EU and US in two other indications, atopic dermatitis and asthma.

The primary safety analysis in this document was conducted using pooled data from adult patients with CRSwNP who received dupilumab 300 mg q2w for 24 weeks in the two pivotal Phase 3 Studies EFC14146 and EFC14280. In this document, the term "safety pool" is used to designate the 24-week pooled data.

Phase 2 Study ACT12340 was not included in the safety pool because it was a Phase 2 proof of concept study in a limited number of patients (30 on dupilumab) with a shorter treatment duration (16 weeks), and with a different dosing regimen (dupilumab 300 mg qw with a loading dose of 600 mg on Day 1) that was not evaluated in Phase 3. All safety data from Study ACT12340 are provided in the CSR that was submitted in the original marketing application for AD, 5.3.5.1 Study ACT12340 of that submission. The data-cut-off date of the submission dossier is 29 August 2018. Along with the safety pool data, supportive safety data from several other sources (including long-term treatment [52 weeks] with dupilumab in Study EFC14280) are provided in this document. These sources are:
1. Long term safety (ie, 52-week treatment period) from Study EFC14280 and data from the follow-up periods for studies EFC14146 and EFC14280.
2. A summary of safety findings in Phase 2 Study ACT12340 is provided in Section 2.5.3 of the dossier.
3. Any SUSAR reported in a patient who was continuing in the 12-week follow-up period (ie, after the 52-week treatment period) of Study EFC14280, and SUSARs reported in ongoing studies in other indications (AD, asthma, EoE, and allergy) are provided in Section 3.4 of the dossier.
4. High level safety summaries of completed studies in other patient populations (AD, asthma, and eosinophilic esophagitis) are provided in Section 9 of the dossier.

Integrated safety database
The integrated evaluation of safety was assessed using a safety pool that included data up to 24 weeks for all treated patients in the two dupilumab pivotal Phase 3 studies in patients with CRSwNP, EFC14146 and EFC14280 (Table 2).

Table 2 - 24-week placebo-controlled data pool for integrated summary of safety

Treatment	EFC14146 (SINUS-24)	EFC14280 (SINUS-52)	Safety Pool 24 Weeks	Purpose
Placebo	132	150	282	Pooled safety assessment of the primary 300 mg q2w dose regimen versus placebo in the intended indication
Dupilumab 300 mg q2w	143	297[a]	440	

a Patients from EFC14280 treatment arms A (dupilumab 300 mg q2w) and B (dupilumab 300 q2w for the first 24 weeks)

The pooled safety data comprises those from adult patients with CRSwNP who received dupilumab 300 mg q2w for 24 weeks without data from the phase 2 proof-of-concept study due to a shorter treatment period and another dosing regimen. The pooling strategy is endorsed.

Patient exposure

The dupilumab clinical development program for the treatment of patients (≥18 years old) with CRSwNP includes one Phase 2 placebo-controlled study (ACT12340) and two Phase 3 placebo-controlled studies (EFC14146 and EFC14280). All studies were randomized, double-blind, placebo-controlled, parallel group studies.
All patients randomized in studies EFC14146 (N=276) and EFC14280 (N=448) completed (or prematurely discontinued treatment) within the planned treatment period, 24 weeks and 52 weeks, respectively, at the time of the primary database lock for each study. Furthermore, all 276 randomized patients in EFC14146 completed (or prematurely discontinued) the 24-week follow-up period, while at the time of the initial submission 12-week safety follow-up data from 260 patients in EFC14280 were not available, these data through to 16 November 2018 (last patient last study visit) were submitted with the responses to the RSI. No patient was exposed to treatment after the initial data cut-off (29 August 2018) for the initial type 2 variation.

There is only 1 dupilumab group in the 24-week safety pool. As such, from this point forward the "dupilumab 300 mg q2w group" is referred to as the "dupilumab group" in the body of the report. However, the heading "dupilumab 300 mg q2w" is used in the in-text tables and the appendix tables.

Patient disposition
The safety pool comprised 722 randomized patients who received either dupilumab (440 patients) or placebo (282 patients) (Table 11). Of these patients, 425 (96.6%) patients in the dupilumab group and 256 (90.8%) patients in the placebo group completed 24 weeks of treatment. The percentage of patients who decided to voluntarily withdraw from study treatment was lower in the dupilumab group (1.8%) versus the placebo group (7.1%). The proportion of patients who permanently discontinued treatment due to treatment period AEs was lower in the dupilumab group (2.0% [9 patients]) compared with the placebo group (4.6% [13 patients]).

Table 11 - Patient disposition - 24 week pooled safety population

	Placebo (N=282)	Dupilumab 300mg q2w[a] (N=440)
Randomized and treated	282 (100%)	440 (100%)
Completed 24-weeks treatment	256 (90.8%)	425 (96.6%)
Discontinued treatment prior to week 24	26 (9.2%)	15 (3.4%)
Subject's decision for treatment discontinuation	20 (7.1%)	8 (1.8%)
Main reason for permanent treatment discontinuation		
Adverse event	13 (4.6%)	9 (2.0%)
Lack of efficacy	4 (1.4%)	1 (0.2%)
Poor compliance to protocol	1 (0.4%)	0
Other reason	8 (2.8%)	5 (1.1%)
Withdrew from study prior to week 24	7 (2.5%)	5 (1.1%)
Main reason for study discontinuation		
Adverse event	2 (0.7%)	3 (0.7%)
Poor compliance to protocol	0	0
Other reason	5 (1.8%)	2 (0.5%)

Note: percentages are calculated using the number of patients treated as denominator
[a] All patients from EFC14146 and EFC14280 treated with 300 mg q2w, in either treatment group 300 mg q2w or 300 mg q2w-q4w.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/dis_dispo_by24_s_t.sas
OUT=REPORT/OUTPUT/dis_dispo_by24_s_t_i.rtf (12OCT2018 - 11:57)

Of the 722 patients included in the safety population, 719 (99.6%) patients had at least one Non-missing result in the ADA assay following the first dose of the study drug and thus were included in the ADA population.

Exposure to IMP in the safety pool, expressed as number exposed and in patient-years (PY) of exposure, is provided in Table 13, along with the contribution from each study separately. Overall exposure was higher in the dupilumab group (198.06 PY) compared with the placebo group (124.76 PY) due to the additional dupilumab treatment arm in Study EFC14280.

Table 13 - Patient-years exposure to investigational medicinal product by study - 24 week pooled safety population

Studies	Placebo	Dupilumab 300mg q2w[a]
EFC14146		
N=exposed	132	143
Patient yrs	58.75	64.06
EFC14280		
N=exposed	150	297
Patient yrs	66.01	134.00
All		
N=exposed	282	440
Patient yrs	124.76	198.06

[a] All patients from EFC14146 and EFC14280 treated with 300 mg q2w, in either treatment group 300 mg q2w or 300 mg q2w-q4w.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/cdc_exposure_bystudy_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_bystudy_by24_s_t_i.rtf (12OCT2018 - 11:53)

In the safety pool, the median duration of treatment exposure was 168 days in the dupilumab and

placebo treatment groups (Table 14).
Please note that for patients in Study EFC14146 the last injection of study treatment was at Week 22 (total of 12 injections), whereas for Study EFC14280, patients continued to be treated after Week 22 and received an additional injection at Week 24 for a total of 13 injections.

Table 14 - Exposure to investigational medicinal product - 24 week pooled safety population

	Placebo (N=282)	Dupilumab 300mg q2w[a] (N=440)
Cumulative exposure to treatment (patient years)	124.8	198.1
Duration of study treatment (days)		
Number	282	440
Mean (SD)	161.59 (23.19)	164.42 (19.70)
Median	168.00	168.00
Q1 : Q3	168.00 : 168.00	168.00 : 168.00
Min : Max	14.0 : 168.0	14.0 : 168.0
Duration of study treatment by category [n(%)]		
> 0 and ≤ 4 weeks	2 (0.7%)	3 (0.7%)
> 4 and ≤ 8 weeks	4 (1.4%)	3 (0.7%)
> 8 and ≤ 12 weeks	1 (0.4%)	6 (1.4%)
> 12 and ≤ 16 weeks	8 (2.8%)	2 (0.5%)
> 16 and ≤ 20 weeks	8 (2.8%)	0
> 20 and < 24 weeks - 3 days	5 (1.8%)	3 (0.7%)
≥ 24 weeks - 3 days and ≤ 24 weeks	254 (90.1%)	423 (96.1%)
Cumulative duration of study treatment by category [n(%)]		
> 0 week	282 (100%)	440 (100%)
> 4 weeks	280 (99.3%)	437 (99.3%)
> 8 weeks	276 (97.9%)	434 (98.6%)
> 12 weeks	275 (97.5%)	428 (97.3%)
> 16 weeks	267 (94.7%)	426 (96.8%)
> 20 weeks	259 (91.8%)	426 (96.8%)
≥ 24 weeks - 3 days	254 (90.1%)	423 (96.1%)

	Placebo (N=282)	Dupilumab 300mg q2w[a] (N=440)
Number of injections[b] [n(%)]		
1 injection	1 (0.4%)	3 (0.7%)
2 injections	2 (0.7%)	0
3 injections	2 (0.7%)	3 (0.7%)
4 injections	2 (0.7%)	1 (0.2%)
5 injections	0	2 (0.5%)
6 injections	1 (0.4%)	3 (0.7%)
7 injections	1 (0.4%)	2 (0.5%)
8 injections	9 (3.2%)	0
9 injections	4 (1.4%)	0
10 injections	5 (1.8%)	1 (0.2%)
11 injections	9 (3.2%)	22 (5.0%)
12 injections	153 (54.3%)	211 (48.0%)
13 injections	93 (33.0%)	192 (43.6%)

Note: Patients are considered in the treatment group they actually received. The extent of IMP exposure is summarized by the duration of IMP exposure, defined as last dose date - first dose date + 14 days, regardless of unplanned intermittent discontinuations.

a All patients from EFC14146 and EFC14280 treated with 300 mg q2w, in either treatment group 300 mg q2w or 300 mg q2w-q4w.

b For patients from EFC14146, the last scheduled injection is injection 12 at week 22, while patients in the 52 week study EFC14280, continue treatment and thus receive an injection 13 at week 24.

PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/cdc_exposure_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_by24_s_t_i.rtf (12OCT2018 - 11:55)

Given that the majority of patients were 18 to 64 years of age (82.8%), were Caucasian/White (87.8%), and males (60.2%) (Table 17), exposure to study treatment was highest in those categories: 18 to 64 year of age (162.65 PY in the dupilumab group and 104.79 PY in the placebo group); Caucasian/White patients (172.58 PY in the dupilumab group and 111.02 PY in the placebo group) and male patients (121.94 PY in the dupilumab group and 72.73 PY in the placebo group). By region, exposure was highest in Western countries (87.61 PY in the dupilumab group and 53.85 PY in the placebo group). Western countries included Australia, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom, and the US. Exposure in patients with asthma was 117.28 PY in the dupilumab group and 72.38 PY in the placebo group and in patients with asthma and/or NSAID-ERD exposure was 124.18 PY in the dupilumab group and 76.05 PY in the placebo group.

MFNS compliance

On a daily basis throughout each study, MFNS was self-administered and the patient reported the amount taken in an e-diary. Mean overall compliance to MFNS during treatment was similar in the dupilumab and placebo treatment groups (92.04% and 92.05%, respectively). As per the protocols for studies EFC14146 and EFC14280, all patients were to receive 2 actuations of MFNS (50 µg/actuation) in each nostril twice daily (BID) for a total daily dose of 400 µg. However, patients showing poor tolerance to BID dosing were allowed to receive a lower dose regimen of MFNS (200 µg) once daily. In the dupilumab and placebo groups approximately 87% (630 of 722) of patients received BID dosing.

Mean compliance to MFNS was similar in the dupilumab and placebo groups for patients who were prescribed MFNS BID at randomization (91.02% and 91.44%, respectively) and for those who were prescribed MFNS QD at randomization (98.51% and 96.76%, respectively).

Demographics

Overall, demographic and baseline characteristics were generally similar between the dupilumab and placebo treatment groups in the safety pool. The mean (SD) age of all patients (N=722) was 51.4 (12.8) years; 17.1% of patients were elderly (≥65 years of age) and 19 (2.6%) patients were ≥75 years. Overall, 60.2% of patients were men and 39.8% were women. A majority of patients were White (87.8%) and non-Hispanic (80.8%); approximately 7.6% were Asian and 2.2% were Black. Of all patients enrolled, 30.9% had a BMI ≥30 kg/m2 and 29.9% had body weight ≥90 kg. The enrolled population was distributed globally with 44.5% from sites in Western countries, 29.8% from East Europe, 19.0% from Latin America, and 6.8% from Asia.

Disease characteristics at baseline

The patients' disease characteristics at baseline indicate that the patients enrolled had severe CRSwNP, as evidenced by significant nasal polyp size, significant symptoms, poor baseline sense of smell, extensive sinus disease, and poor QOL. There were no meaningful imbalances in disease characteristics between the treatment arms.

At baseline, the mean endoscopic bilateral NP score was 6.00 in the dupilumab group and 5.92 in the placebo group (range of total score is 0-8, lower scores indicate smaller-sized polyps); mean nasal congestion/obstruction score was 2.39 and 2.42, respectively (range of scale is 0-3, lower scores indicate less symptoms), mean sino-nasal outcome test (SNOT-22) score was 50.12 and 52.19, respectively (range of global score is 0-110, lower scores indicate less impact of nasal symptoms and social/emotional consequences of the patient's nasal disorder), and the University of Pennsylvania Smell Identification Test (UPSIT) mean results were 13.91 and 14.08, respectively (range of scale is 0-40, where a lower score indicates worse olfaction). Most patients in both treatment groups had extensive opacification of the sinuses bilaterally as assessed by the LMK CT scan total mean score, was 18.26 and 18.55, respectively (total score range is 0-24, higher scores indicate more sinus opacification). Mean VAS of overall rhinosinusitis severity was 7.83 in the dupilumab group and 7.96 in the placebo group (range 0-10, higher score indicates greater severity, >7 indicates severe disease).

At baseline, 57.6% of patients in the dupilumab group and 60.6% of patients in the placebo group had blood eosinophil counts ≥0.3 Giga/L signifying the systemic type 2 inflammation that is typical of CRSwNP.

Medical history

Chronic rhinosinusitis with nasal polyposis

The mean time since the first diagnosis of CRSwNP was approximately 11 years. The mean age at onset was 40.5 years. Overall, 63.4% of patients had undergone at least one prior surgery for nasal polyps: 62.0% in the dupilumab group and 65.6% in the placebo group. The proportion of patients in the dupilumab and placebo groups who had 3 or more NP surgeries was 23.4% and 24.9%, respectively. Mean time since the most recent NP surgery was similar between the dupilumab and placebo groups
(7.23 and 7.06 years, respectively).
In the 2 years prior to randomization, 74.5% of patients were treated with SCS. The mean number of SCS courses in the past 2 years was 1.60 and 1.48 for the dupilumab and placebo groups, respectively, with approximately 30% of these patients receiving 2 or more courses of SCS. The median number of days of SCS use was 11.0 days with 37.6% of patients receiving SCS for ≤14 days. Overall, the history of SCS use was comparable between the dupilumab and placebo groups. A history of epistaxis was reported by 15.5% of patients in the dupilumab group and 15.6% of patients in the placebo group.

Asthma and NSAID-ERD

Overall, 59.1% of patients had a history of asthma. The mean age at onset of asthma was 34.8 years. The mean time since the first diagnosis of asthma was 16.9 years and the mean time since the last asthma exacerbation was 56.3 months. Mean baseline percent predicted FEV1 was 84.12%. The mean ACQ-6 at baseline was 1.59 and the median ACQ-6 was 1.5, indicating that half of the patients had uncontrolled asthma. The mean number of severe asthma exacerbations in the previous year was 0.43. Most patients with asthma (90.8%) were on asthma medication during the year prior to starting study drug, with the majority (73.8%) of patients using both ICS and LABA at baseline. Overall, 28.1% of patients had NSAID-ERD, with a majority (87.2% [177 of 203]) of these patients having conditional NSAID-ERD which was based solely on the patient's clinical history.

Other type 2 inflammatory diseases

A patient was considered to have a comorbid type 2 inflammatory disease including atopic history or ongoing comorbid disease if the patient had any of the following diseases: AD, allergic conjunctivitis, allergic rhinitis (including seasonal and perennial rhinitis), eosinophilic esophagitis, food allergy, and/or hives. At baseline, the majority of patients had a comorbid type 2 inflammatory disease: 79.8% (including asthma/NSAID-ERD) and 62.0% (excluding asthma/NSAID-ERD). The most frequently reported atopic condition was allergic rhinitis (57.6%).

Prior medications

Most patients (81.7%) were taking intranasal corticosteroid medications in the year before screening. The most commonly used prior intranasal corticosteroid medications included mometasone/mometasone furoate (9.1% and 38.1%, respectively), fluticasone propionate (14.5%), budesonide (8.9%), fluticasone furoate (8.7%), and fluticasone (4.6%).
All patients were on a stable dose of intranasal MFNS at randomization. Most patients were on BID dosing at randomization (86.4% [dupilumab] and 88.7% [placebo]). For patients with a history of asthma, a similar proportion of patients in the dupilumab and placebo treatment groups received any ICS/LABA controller medication within 1 year prior to screening (78.1% [203 patients] and 81.4% [136 patients], respectively).

Adverse events

a) Safety pool (studies EFC14146 and EFC14280 through week 24)

Overall summary of treatment emergent period adverse events

The percentage of patients with at least 1 treatment period AE was lower in the dupilumab group compared with the placebo group (69.3% versus 73.8%). The same trend was observed for SAEs

(3.4% versus 5.7%) and for patients who had AEs that resulted in permanent treatment discontinuation (2.5% versus 5.3%) (Table 22).
No deaths were reported in the 24-week treatment period of the safety pool. Outside of the 24-week treatment period, however, two deaths occurred: one placebo-treated patient died due to suspected myocardial infarction in the post-treatment period of Study EFC14146 and one patient in the dupilumab 300 mg q2w-q4w group in Study EFC14280 died due to a traumatic intracranial hemorrhage 72 days after the last dose of IMP. These were the only deaths reported in the CRSwNP studies (EFC14146, EFC14280, and ACT12340).

Table 22 - Overview of adverse event profile - 24 week pooled safety population

n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Patients with any AE	208 (73.8%)	305 (69.3%)
Patients with any severe AE	18 (6.4%)	17 (3.9%)
Patients with any SAE	16 (5.7%)	15 (3.4%)
Patients with any AE leading to death	0	0
Patients with any AE leading to permanent treatment discontinuation	15 (5.3%)	11 (2.5%)
Patients with any treatment-related AE	46 (16.3%)	88 (20.0%)

AE: Adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product
n (%) = number and percentage of patients with at least one AE
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_overview_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_by24_s_t_i.rtf (12OCT2018 - 14:17)

The percentage of patients experiencing common AEs (defined as AEs with PT incidence ≥1% in either treatment group) during the treatment period is provided in Table 23. The infections and infestations SOC had the highest proportion of patients with AEs; the incidence was 10.6% lower in the dupilumab group (32.0%) compared with the placebo group (42.6%) with a relative risk of 0.70 (95% CI: 0.58 to 0.85) (Table 24). The most frequently reported PT in both groups was nasopharyngitis (12.5% in the dupilumab group and 14.5% in the placebo group).

The respiratory, thoracic and mediastinal disorders SOC had the second highest proportion of patients with AEs, with a 11.9% lower incidence in the dupilumab group compared to the placebo group (18.2% versus 30.1%, respectively), with a relative risk of 0.59 (95% CI: 0.45 to 0.77) (Table 24). In this SOC, the most frequently reported PTs in the dupilumab and placebo groups were epistaxis (5.7% and 7.1%, respectively), cough (3.4% and 3.2%, respectively), nasal polyps (2.7% and 11.7%, respectively), and asthma (1.6% and 7.1%, respectively). The general disorders and administration site conditions SOC had the third highest proportion of patients with AEs (mainly due to injection site reactions); incidence was similar in the dupilumab and placebo groups (19.1% and 17.7%, respectively). The most frequently reported PTs in the dupilumab and placebo groups were injection site erythema (6.4% and 7.8%, respectively) and injection site reaction (3.4% and 1.8%, respectively).

In the safety pool, TEAEs reported at a higher incidence in the dupilumab group than in the placebo group by at least 1 percentage point were:
- Injection site reaction (3.4% versus 1.8%)
- Arthralgia (3.2% versus 1.8%)
- Hypertension (2.7% versus 1.1%)
- Insomnia (1.4% versus 0%)
- Conjunctivitis (1.4% versus 0%)
- Injection site swelling (1.4% versus 0.4%)

Injection site reactions and events of injection site swelling were mostly mild to moderate; there was 1 severe case. No patients had a SAE due to an injection site reaction and no patient discontinued as a result of an injection site reaction/swelling. All injection site reactions resolved or were resolving despite continued use of dupilumab.

In the safety pool through 24 weeks for treatment, arthralgia was reported in 3.2% (14 patients) in the dupilumab group versus 1.8% (5 patients) in the placebo group. The relative risk ratio (95% CI) for dupilumab versus placebo was 1.73 (0.59 to 5.03).
Other PTs in the musculoskeletal and connective tissue disorders SOC that were reported in 3 patients or more in either treatment group with a higher incidence in the dupilumab group than in the placebo group were musculoskeletal pain (0.9% [4 patients] versus 0.4% [1 patient], respectively), neck pain (0.9% [4 patients] versus 0.4% [1 patient, respectively), and joint swelling (0.7% [3 patients] versus 0%, respectively).
PTs reported with a higher incidence in the placebo group than in the dupilumab group were myalgia (1.4% [4 patients] versus 0.9% [4 patients], respectively) and pain in extremity (1.4% [4 patients] versus 0.5% [2 patients], respectively). Incidence of back pain was similar in the dupilumab and placebo treatment groups (2.7% [12 patients] and 2.5% [7 patients], respectively).

Through the complete treatment-emergent periods across both studies, there were 22 dupilumab-treated patients (combined groups [q2w plus q2w-q4w]) and 5 placebo-treated patients who reported arthralgia, for a combined incidence of 5.0% for dupilumab versus 1.8% for placebo.

Of the 22 cases of arthralgias on dupilumab, 21 of these were mild to moderate and recovered with oral non-steroidal anti-inflammatory therapy. Only 2 of these patients had ADA (both low titer). There was one severe case of arthralgia considered related to study treatment which occurred in a dupilumab-treated patient. This patient had a syndrome consisting of eosinophilia, arthralgia, asthma exacerbation and insomnia which occurred in association with reduction in oral corticosteroid use.

The PT "hypertension" was reported in 12 (2.7%) patients in the dupilumab group versus 3 (1.1%) patients in the placebo group. No events were considered as serious, severe or resulted in permanent study drug discontinuation.
Evaluation of the HLGT "vascular hypertensive disorders" which captures all hypertension-related PTs in the vascular disorders SOC, showed similar frequencies in the dupilumab and placebo groups (2.7% and 2.8%, respectively).
Insomnia was reported in 1.4% [6 patients] in the dupilumab group versus no patients in the placebo group. The events were mostly mild (5/6 cases). Most (4/6) insomnia events resolved. Insomnia in dupilumab-treated patients contributed to the imbalance observed in the Psychiatric disorders SOC overall (3.9% [17 patients] versus 0.7% [2 patients] placebo). However, there was no evidence for concomitant psychiatric diagnoses such as anxiety or consistent association of other AEs with insomnia.

An imbalance between dupilumab and placebo was observed for conjunctivitis (1.4% [6 patients] versus no placebo patients). There were no cases of keratitis reported in CRSwNP patients.

TEAEs reported at a higher incidence in the placebo group than in the dupilumab group by at least 1 percentage point were: nasopharyngitis (14.5% versus 12.5%), nasal polyps (11.7% versus 2.7%), headache (8.5% versus 7.3%), injection site erythema (7.8% versus 6.4%), asthma (7.1% versus 1.6%), epistaxis (7.1% versus 5.7%), upper respiratory tract infection (5.0% versus 3.0%), acute sinusitis (4.6% versus 1.4%), sinusitis (4.3% versus 1.1%), accidental overdose (3.5% versus 2.5%), otitis media (1.8% versus 0.5%), lower respiratory tract infection (1.8% versus 0.2%), abdominal pain upper (1.8% versus 0.7%), hypertensive crisis (1.4% versus 0%), ear infection (1.4% versus 0.2%), nasal obstruction (1.4% versus 0.2%), intentional overdose (1.1% versus 0%), and otosalpingitis (1.1% versus 0%). Consistent with the clinical presentation and common complications in patients with uncontrolled CRSwNP and its associated comorbidity asthma, most of the TEAEs more frequently reported in the placebo group were related to upper and lower airway diseases, ear disorders, and asthma. Others, however, appear to be random variation: accidental overdose, abdominal pain, hypertensive crisis, and intentional overdose.

Table 23 - Number (%) of patients with common AE(s), PT ≥1% in either treatment group, by primary SOC and PT - 24 week pooled safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Any class	208 (73.8%)	305 (69.3%)
Infections and infestations	120 (42.6%)	141 (32.0%)
Nasopharyngitis	41 (14.5%)	55 (12.5%)
Upper respiratory tract infection	14 (5.0%)	13 (3.0%)
Bronchitis	9 (3.2%)	10 (2.3%)
Pharyngitis	5 (1.8%)	8 (1.8%)
Influenza	4 (1.4%)	7 (1.6%)
Acute sinusitis	13 (4.6%)	6 (1.4%)
Conjunctivitis	0	6 (1.4%)
Oral herpes	2 (0.7%)	6 (1.4%)
Sinusitis	12 (4.3%)	5 (1.1%)
Urinary tract infection	5 (1.8%)	4 (0.9%)
Gastroenteritis	3 (1.1%)	3 (0.7%)
Otitis media	5 (1.8%)	2 (0.5%)
Rhinitis	3 (1.1%)	2 (0.5%)
Chronic sinusitis	3 (1.1%)	1 (0.2%)
Ear infection	4 (1.4%)	1 (0.2%)
Lower respiratory tract infection	5 (1.8%)	1 (0.2%)
Otitis media acute	3 (1.1%)	1 (0.2%)
Respiratory tract infection	3 (1.1%)	1 (0.2%)
Otosalpingitis	3 (1.1%)	0

Blood and lymphatic system disorders	3 (1.1%)	8 (1.8%)
Eosinophilia	1 (0.4%)	5 (1.1%)
Psychiatric disorders	2 (0.7%)	17 (3.9%)
Insomnia	0	6 (1.4%)
Nervous system disorders	34 (12.1%)	45 (10.2%)
Headache	24 (8.5%)	32 (7.3%)
Dizziness	3 (1.1%)	3 (0.7%)
Vascular disorders	15 (5.3%)	14 (3.2%)
Hypertension	3 (1.1%)	12 (2.7%)
Hypertensive crisis	4 (1.4%)	0
Respiratory, thoracic and mediastinal disorders	85 (30.1%)	80 (18.2%)
Epistaxis	20 (7.1%)	25 (5.7%)
Cough	9 (3.2%)	15 (3.4%)
Nasal polyps	33 (11.7%)	12 (2.7%)
Asthma	20 (7.1%)	7 (1.6%)
Oropharyngeal pain	3 (1.1%)	6 (1.4%)
Rhinorrhoea	2 (0.7%)	6 (1.4%)
Nasal congestion	4 (1.4%)	3 (0.7%)
Nasal obstruction	4 (1.4%)	1 (0.2%)
Gastrointestinal disorders	37 (13.1%)	59 (13.4%)
Gastritis	2 (0.7%)	7 (1.6%)
Gastrooesophageal reflux disease	2 (0.7%)	6 (1.4%)
Nausea	3 (1.1%)	5 (1.1%)
Toothache	1 (0.4%)	5 (1.1%)
Abdominal pain	3 (1.1%)	4 (0.9%)
Dental caries	3 (1.1%)	4 (0.9%)
Diarrhoea	4 (1.4%)	4 (0.9%)
Vomiting	5 (1.8%)	4 (0.9%)
Abdominal pain upper	5 (1.8%)	3 (0.7%)
Skin and subcutaneous tissue disorders	18 (6.4%)	26 (5.9%)
Rash	3 (1.1%)	4 (0.9%)
Erythema	3 (1.1%)	3 (0.7%)
Musculoskeletal and connective tissue disorders	26 (9.2%)	53 (12.0%)
Arthralgia	5 (1.8%)	14 (3.2%)

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Back pain	7 (2.5%)	12 (2.7%)
Myalgia	4 (1.4%)	4 (0.9%)
Pain in extremity	4 (1.4%)	2 (0.5%)
General disorders and administration site conditions	50 (17.7%)	84 (19.1%)
Injection site erythema	22 (7.8%)	28 (6.4%)
Injection site reaction	5 (1.8%)	15 (3.4%)
Injection site pain	4 (1.4%)	8 (1.8%)
Injection site swelling	1 (0.4%)	6 (1.4%)
Fatigue	4 (1.4%)	5 (1.1%)
Injection site bruising	2 (0.7%)	5 (1.1%)
Pyrexia	3 (1.1%)	5 (1.1%)
Oedema peripheral	3 (1.1%)	2 (0.5%)
Injury, poisoning and procedural complications	27 (9.6%)	36 (8.2%)
Accidental overdose	10 (3.5%)	11 (2.5%)
Intentional overdose	3 (1.1%)	0

AE: Adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one AE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group.
Only PTs at least 1% in at least one group are presented.
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_freq1_by24_s_t_i.rtf (12OCT2018 - 14:18)

Table 24 – Incidence rate of all AEs with PT≥2% and ≥1% higher incidence in one of the groups compared to the other, with relative risk ratio (95% CI) for dupilumab 300 mg q2w versus placebo, by primary SOC and PT – 24 week pooled safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)	Relative risk ratio (95% CI) dupilumab 300mg q2w vs placebo	P-value vs. placebo
Any Class	208 (73.8%)	305 (69.3%)	0.91 (0.83 to 1.00)	
Infections and infestations	120 (42.6%)	141 (32.0%)	0.70 (0.58 to 0.85)	
Nasopharyngitis	41 (14.5%)	55 (12.5%)	0.84 (0.57 to 1.23)	0.3611
Upper respiratory tract infection	14 (5.0%)	13 (3.0%)	0.52 (0.25 to 1.10)	0.0826
Acute sinusitis	13 (4.6%)	6 (1.4%)	0.25 (0.09 to 0.66)	0.0025
Sinusitis	12 (4.3%)	5 (1.1%)	0.21 (0.08 to 0.61)	0.0014
Nervous system disorders	34 (12.1%)	45 (10.2%)	0.82 (0.53 to 1.25)	
Headache	24 (8.5%)	32 (7.3%)	0.81 (0.48 to 1.36)	0.4259
Vascular disorders	15 (5.3%)	14 (3.2%)	0.64 (0.30 to 1.33)	
Hypertension	3 (1.1%)	12 (2.7%)	2.70 (0.74 to 9.92)	0.1180
Respiratory, thoracic and mediastinal disorders	85 (30.1%)	80 (18.2%)	0.59 (0.45 to 0.77)	
Epistaxis	20 (7.1%)	25 (5.7%)	0.77 (0.45 to 1.34)	0.3574
Nasal polyps	33 (11.7%)	12 (2.7%)	0.25 (0.13 to 0.48)	<.0001
Asthma	20 (7.1%)	7 (1.6%)	0.19 (0.08 to 0.48)	<.0001
General disorders and administration site conditions	50 (17.7%)	84 (19.1%)	1.07 (0.78 to 1.48)	
Injection site erythema	22 (7.8%)	28 (6.4%)	0.82 (0.47 to 1.43)	0.4798
Injection site reaction	5 (1.8%)	15 (3.4%)	1.75 (0.63 to 4.92)	0.2770
Injury, poisoning and procedural complications	27 (9.6%)	36 (8.2%)	0.84 (0.52 to 1.36)	
Accidental overdose	10 (3.5%)	11 (2.5%)	0.68 (0.29 to 1.59)	0.3724

Confidence intervals are Cochran-Mantel-Haenszel stratified by study.
MEDDRA 21.0
n (%) = number and percentage of patients with at least one AE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group.
Only PTs at least 2% in at least one group are presented.
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.

A forest plot of relative risk ratio of all treatment period AEs with PT ≥2% and ≥1% higher incidence in one of the groups compared to the other was provided. Three terms showed increased relative risk for dupilumab compared to placebo: PT hypertension, PT injection site reaction and PT arthralgia.
In all cases the lower bound of the 95% CI of relative risk was <1, therefore not demonstrating a significant difference from placebo (given the frequency of the PTs).

In contrast, several terms showed decreased relative risk for dupilumab compared to placebo. Four of these, PTs nasal polyps, acute sinusitis, sinusitis, and asthma showed significantly lowered RR (upper bound of 95% CI of relative risk <1) suggesting a protective effect of dupilumab on appearance of these upper and lower airway events that are often associated with poorly controlled CRSwNP disease.

Treatment period adverse events by Investigator causality
The proportion of patients with treatment period AEs related to IMP per the investigator was 20.0% in the dupilumab group and 16.3% in the placebo group (cf table 25). The general disorders and administration site conditions SOC had the highest proportion of patients with treatment-related AEs. The incidence was numerically higher in the dupilumab group (14.8%) compared with the placebo group (12.1%). The most frequently reported PTs in the dupilumab and placebo groups were injection site erythema (6.1% and 7.4%, respectively) and injection site reaction (3.4% and 1.8%, respectively).

Table 25 - Number (%) of patients with AE(s) related to IMP by primary SOC and PT - 24 week pooled safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Any class	46 (16.3%)	88 (20.0%)
Infections and infestations	1 (0.4%)	2 (0.5%)
Bronchitis	0	1 (0.2%)
Otitis media acute	0	1 (0.2%)
Nasopharyngitis	1 (0.4%)	0
Blood and lymphatic system disorders	1 (0.4%)	5 (1.1%)
Eosinophilia	0	5 (1.1%)
Leukocytosis	0	1 (0.2%)
Pernicious anaemia	1 (0.4%)	0
Immune system disorders	0	2 (0.5%)
Drug hypersensitivity	0	1 (0.2%)
Eosinophilic granulomatosis with polyangiitis	0	1 (0.2%)
Metabolism and nutrition disorders	1 (0.4%)	1 (0.2%)
Increased appetite	1 (0.4%)	1 (0.2%)
Psychiatric disorders	1 (0.4%)	2 (0.5%)
Insomnia	0	1 (0.2%)
Listless	0	1 (0.2%)
Anxiety	1 (0.4%)	0

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Nervous system disorders	1 (0.4%)	6 (1.4%)
Headache	0	3 (0.7%)
Parosmia	0	2 (0.5%)
Cerebral infarction	0	1 (0.2%)
Dizziness	1 (0.4%)	0
Eye disorders	1 (0.4%)	1 (0.2%)
Dry eye	0	1 (0.2%)
Eye inflammation	1 (0.4%)	0
Cardiac disorders	1 (0.4%)	0
Palpitations	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	5 (1.8%)	5 (1.1%)
Rhinorrhoea	0	2 (0.5%)
Sneezing	0	2 (0.5%)
Asthma	2 (0.7%)	1 (0.2%)
Sinus pain	0	1 (0.2%)
Cough	1 (0.4%)	0
Nasal polyps	2 (0.7%)	0
Gastrointestinal disorders	0	5 (1.1%)
Abdominal discomfort	0	1 (0.2%)
Abdominal pain	0	1 (0.2%)
Abdominal pain upper	0	1 (0.2%)
Diarrhoea	0	1 (0.2%)
Vomiting	0	1 (0.2%)
Skin and subcutaneous tissue disorders	2 (0.7%)	9 (2.0%)
Skin lesion	0	2 (0.5%)
Dermatitis	0	1 (0.2%)
Erythema	1 (0.4%)	1 (0.2%)
Exfoliative rash	0	1 (0.2%)
Pain of skin	0	1 (0.2%)
Psoriasis	0	1 (0.2%)
Rash	0	1 (0.2%)
Skin exfoliation	0	1 (0.2%)
Skin fissures	0	1 (0.2%)
Dermatitis atopic	1 (0.4%)	0

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Musculoskeletal and connective tissue disorders	1 (0.4%)	5 (1.1%)
Arthralgia	0	2 (0.5%)
Joint swelling	0	1 (0.2%)
Lupus-like syndrome	0	1 (0.2%)
Psoriatic arthropathy	0	1 (0.2%)
Rheumatic disorder	0	1 (0.2%)
Muscle spasms	1 (0.4%)	0
Reproductive system and breast disorders	0	1 (0.2%)
Erectile dysfunction	0	1 (0.2%)
General disorders and administration site conditions	34 (12.1%)	65 (14.8%)
Injection site erythema	21 (7.4%)	27 (6.1%)
Injection site reaction	5 (1.8%)	15 (3.4%)
Injection site pain	4 (1.4%)	8 (1.8%)
Injection site swelling	1 (0.4%)	6 (1.4%)
Injection site bruising	2 (0.7%)	5 (1.1%)
Fatigue	1 (0.4%)	3 (0.7%)
Injection site pruritus	0	3 (0.7%)
Injection site rash	0	3 (0.7%)
Injection site urticaria	1 (0.4%)	3 (0.7%)
Injection site warmth	0	2 (0.5%)
Asthenia	0	1 (0.2%)
Injection site dermatitis	0	1 (0.2%)
Injection site exfoliation	0	1 (0.2%)
Injection site haematoma	2 (0.7%)	1 (0.2%)
Injection site haemorrhage	0	1 (0.2%)
Injection site induration	0	1 (0.2%)
Injection site irritation	0	1 (0.2%)
Injection site nodule	0	1 (0.2%)
Injection site oedema	0	1 (0.2%)
Oedema peripheral	0	1 (0.2%)
Pain	0	1 (0.2%)
Chills	1 (0.4%)	0
Injection site discolouration	1 (0.4%)	0
Injection site hypersensitivity	1 (0.4%)	0
Injection site inflammation	1 (0.4%)	0
Investigations	0	2 (0.5%)
Blood creatine phosphokinase increased	0	1 (0.2%)
Weight increased	0	1 (0.2%)
Injury, poisoning and procedural complications	3 (1.1%)	6 (1.4%)
Accidental overdose	2 (0.7%)	5 (1.1%)
Ankle fracture	0	1 (0.2%)
Intentional overdose	1 (0.4%)	0

AE: Adverse event, SOC: System organ class, PT: Preferred term, IMP: Investigational medicinal product
MEDDRA 21.0
n (%) = number and percentage of patients with at least one AE related to IMP
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group.
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_imp_bv24_s_t_i.rtf (12OCT2018 - 14:18)

Serious adverse event/deaths/other significant events

For approximately 93% (468/503) of all patients who had any treatment period AE, the maximum intensity was mild or moderate. A lower proportion of patients in the dupilumab group compared to patients in the placebo group experienced a severe AE(s) (3.9% versus 6.4%, respectively) (Table 22).

Overall, the most frequently reported severe AE was nasal polyps with 8 patients reporting the event: 2 patients (0.5%) in the dupilumab group and 6 patients (2.1%) in the placebo group. Most of the other severe PTs were of a single occurrence in a treatment group.

Deaths

No deaths were reported in the safety pool population through 24 weeks of treatment from the two Phase 3 studies. In the individual Phase 3 CRSwNP studies (EFC14146 and EFC14280), a total of 2 deaths were reported. One of the deaths occurred in the post-treatment period and the other death occurred during the treatment emergent period.
Brief narratives for these patients are provided below.
• One Patient was 76-year-old male patient (placebo-treated), who never smoked and had history of asthma and type 2 diabetes mellitus and who experienced an AE of severe intensity leading to death, reported as 'suspected acute myocardial infarction' (**acute myocardial infarction**) on Day 277, 122 days after last (12th) dose of IMP. Sixteen days prior to receiving the first dose of IMP, the patient had an AE of 'hypertension (newly diagnosed)'. Corrective treatment included oral lisinopril. On Day 136 of the study (9 days after the 10th IMP injection), the patient had an AE of moderate intensity, reported as 'swollen left leg due to deep vein thrombosis in the left popliteal vein extending into the distal femoral vein' (deep vein thrombosis). Corrective treatment included oral rivaroxaban with recovery on Day 253. On Day 274, the patient reported persistent breathlessness and his asthma inhaler was switched to beclomethasone/formoterol. On Day 277, the patient was found dead in his home by the emergency services. Essential hypertension and type 2 diabetes mellitus were considered as secondary causes of death.
An autopsy was not performed. The event was not related to the IMP as per the investigator's assessment.

• The other Patient was a 78-year-old male patient (dupilumab 300 mg q2w-q4w) with a medical history of asthma, osteoporosis, and allergic rhinitis who experienced a severe **traumatic intracranial haemorrhage** (subdural and subarachnoid hemorrhage, massive brain edema, fracture of the right petrous bone) due to accidental fall from a bike, occurring on Day 422, 72 days after the last (26th) IMP injection. This patient died on Day 423, due to traumatic intracranial hemorrhage and neurotrauma. Autopsy was not
performed. The event was not related to the IMP as per the investigator's assessment.

Other serious adverse events

In the safety pool, a lower proportion of patients in the dupilumab group compared to patients in the placebo group experienced SAEs (3.4% [15 patients] versus 5.7% [16 patients], respectively).

The most frequently reported SAE in the safety pool was nasal polyps (1 patient in the dupilumab group versus 2 patients in the placebo group); the SAE of asthma was reported in 2 placebo patients only (Table 26). Most other SAEs were single PTs occurrences in either dupilumab or placebo groups. The SAEs that were considered by the investigator to be related to IMP were eosinophilia in one patient and EGPA (EGPA) in another patient and occurred in dupilumab-treated patients. These SAEs were severe in intensity and led to permanent treatment discontinuation in both patients.

Two patients in the dupilumab group reported more than one SAE. One patient experienced 3 events (oesophageal perforation, infectious pleural effusion, and septic shock), all severe in intensity and all due to an ingested fish bone that caused oesophageal perforation. Another patient experienced 2 events (fall and upper limb fracture, both moderate in intensity). The SAEs in these 2 patients were considered by the investigator to be not related to IMP and did not lead to permanent treatment discontinuation.

Three patients in the placebo group reported more than one SAE. One patient experienced 2 events (vitreous haemorrhage and lumbar radiculopathy, both severe in intensity). Another experienced 3 events (facial bones fracture, humerus fracture, and syncope; all severe in intensity) which led to

permanent treatment discontinuation. The last patient experienced 2 events (wound infection and peripheral arterial occlusive disease, both severe in intensity). The SAEs in these 3 patients were considered by the investigator to be not related to IMP.

Table 26 - Number (%) of patients with SAE(s) by primary SOC and PT - 24 week pooled safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Any class	16 (5.7%)	15 (3.4%)
Infections and infestations	3 (1.1%)	3 (0.7%)
Appendicitis	0	1 (0.2%)
Diverticulitis	0	1 (0.2%)
Infectious pleural effusion	0	1 (0.2%)
Septic shock	0	1 (0.2%)
Erysipelas	1 (0.4%)	0
Pneumonia	1 (0.4%)	0
Wound infection	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2%)
Nasal neoplasm benign	0	1 (0.2%)
Blood and lymphatic system disorders	0	1 (0.2%)
Eosinophilia	0	1 (0.2%)
Immune system disorders	0	1 (0.2%)
Eosinophilic granulomatosis with polyangiitis	0	1 (0.2%)
Nervous system disorders	3 (1.1%)	1 (0.2%)
Carpal tunnel syndrome	0	1 (0.2%)
Lumbar radiculopathy	1 (0.4%)	0
Syncope	1 (0.4%)	0
Temporal lobe epilepsy	1 (0.4%)	0
Eye disorders	1 (0.4%)	1 (0.2%)
Retinal vein thrombosis	0	1 (0.2%)
Vitreous haemorrhage	1 (0.4%)	0

Primary System Organ Class Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Ear and labyrinth disorders	1 (0.4%)	0
Deafness neurosensory	1 (0.4%)	0
Cardiac disorders	1 (0.4%)	1 (0.2%)
Acute myocardial infarction	0	1 (0.2%)
Aortic valve stenosis	1 (0.4%)	0
Vascular disorders	1 (0.4%)	0
Peripheral arterial occlusive disease	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	4 (1.4%)	1 (0.2%)
Nasal polyps	2 (0.7%)	1 (0.2%)
Asthma	2 (0.7%)	0
Gastrointestinal disorders	1 (0.4%)	3 (0.7%)
Abdominal pain upper	0	1 (0.2%)
Oesophageal perforation	0	1 (0.2%)
Pancreatitis	0	1 (0.2%)
Abdominal pain	1 (0.4%)	0
Musculoskeletal and connective tissue disorders	0	1 (0.2%)
Osteoarthritis	0	1 (0.2%)
Reproductive system and breast disorders	0	1 (0.2%)
Uterine polyp	0	1 (0.2%)
Investigations	1 (0.4%)	0
Weight decreased	1 (0.4%)	0
Injury, poisoning and procedural complications	2 (0.7%)	1 (0.2%)
Fall	0	1 (0.2%)
Upper limb fracture	0	1 (0.2%)
Facial bones fracture	2 (0.7%)	0
Humerus fracture	1 (0.4%)	0
Social circumstances	1 (0.4%)	0
Miscarriage of partner	1 (0.4%)	0

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one SAE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_sae_by24_s_t_i.rtf (12OCT2018 - 14:17)

Outside of the 24-week safety pool period, there were 2 SAEs which were assessed as potential CV SAEs: a CV death (acute myocardial infarction, placebo) and a non-CV death (traumatic intracranial hemorrhage, dupilumab). There were also 2 placebo-treated patients who experienced SAEs of EGPA in the treatment and post-treatment periods (46 days after the last dose of IMP in Study EFC14280, and 87 days after the last IMP dose in Study EFC14146), respectively.

Since the initial cut-off date for the main report, 3 additional PTs were reported with a frequency ≥2%: tonsillitis (dupilumab q2w group), anosmia (dupilumab q2w-q4w group), and vertigo (placebo group). These additional PTs were added to the list due to single occurrences of AEs in the follow-up period and did not change the overall TEAE profile.

Number (%) of patients with TEAE(s) that occurred with a frequency >=2% in any treatment group by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=150)	300mg q2w-q4w (N=148)	300mg q2w (N=149)
Any class	138 (92.0%)	134 (90.5%)	125 (83.9%)
Infections and infestations	100 (66.7%)	83 (56.1%)	85 (57.0%)
Nasopharyngitis	38 (25.3%)	31 (20.9%)	33 (22.1%)
Upper respiratory tract infection	20 (13.3%)	8 (5.4%)	10 (6.7%)
Bronchitis	8 (5.3%)	9 (6.1%)	9 (6.0%)
Sinusitis	17 (11.3%)	14 (9.5%)	9 (6.0%)
Influenza	6 (4.0%)	7 (4.7%)	7 (4.7%)
Acute sinusitis	16 (10.7%)	5 (3.4%)	5 (3.4%)
Pharyngitis	4 (2.7%)	4 (2.7%)	5 (3.4%)
Gastroenteritis	5 (3.3%)	4 (2.7%)	4 (2.7%)
Conjunctivitis	1 (0.7%)	2 (1.4%)	3 (2.0%)
Tonsillitis	1 (0.7%)	2 (1.4%)	3 (2.0%)
Ear infection	5 (3.3%)	0	2 (1.3%)
Otitis media	6 (4.0%)	1 (0.7%)	2 (1.3%)
Rhinitis	3 (2.0%)	4 (2.7%)	2 (1.3%)
Urinary tract infection	4 (2.7%)	5 (3.4%)	2 (1.3%)
Lower respiratory tract infection	4 (2.7%)	1 (0.7%)	1 (0.7%)
Oral herpes	1 (0.7%)	4 (2.7%)	1 (0.7%)
Periodontitis	3 (2.0%)	1 (0.7%)	1 (0.7%)
Pneumonia	3 (2.0%)	2 (1.4%)	1 (0.7%)
Respiratory tract infection viral	3 (2.0%)	0	1 (0.7%)
Chronic sinusitis	4 (2.7%)	0	0
Cystitis	3 (2.0%)	1 (0.7%)	0
Respiratory tract infection	3 (2.0%)	0	0
Viral upper respiratory tract infection	4 (2.7%)	0	0
Psychiatric disorders	3 (2.0%)	6 (4.1%)	8 (5.4%)
Insomnia	0	0	5 (3.4%)
Nervous system disorders	24 (16.0%)	25 (16.9%)	22 (14.8%)
Headache	18 (12.0%)	17 (11.5%)	14 (9.4%)
Anosmia	0	3 (2.0%)	0
Ear and labyrinth disorders	11 (7.3%)	3 (2.0%)	6 (4.0%)
Ear pain	3 (2.0%)	0	3 (2.0%)
Vertigo	3 (2.0%)	2 (1.4%)	1 (0.7%)
Vascular disorders	7 (4.7%)	6 (4.1%)	8 (5.4%)
Hypertension	2 (1.3%)	6 (4.1%)	7 (4.7%)
Respiratory, thoracic and mediastinal disorders	75 (50.0%)	53 (35.8%)	48 (32.2%)
Epistaxis	20 (13.3%)	8 (5.4%)	13 (8.7%)
Cough	8 (5.3%)	9 (6.1%)	9 (6.0%)
Nasal polyps	29 (19.3%)	21 (14.2%)	9 (6.0%)
Asthma	20 (13.3%)	15 (10.1%)	8 (5.4%)
Nasal congestion	7 (4.7%)	2 (1.4%)	3 (2.0%)
Rhinorrhoea	2 (1.3%)	3 (2.0%)	3 (2.0%)
Nasal obstruction	3 (2.0%)	1 (0.7%)	1 (0.7%)
Chronic rhinosinusitis with nasal polyps	3 (2.0%)	0	0

Gastrointestinal disorders	30 (20.0%)	37 (25.0%)	27 (18.1%)
Abdominal pain	2 (1.3%)	2 (1.4%)	3 (2.0%)
Gastritis	3 (2.0%)	6 (4.1%)	3 (2.0%)
Nausea	2 (1.3%)	2 (1.4%)	3 (2.0%)
Toothache	2 (1.3%)	2 (1.4%)	3 (2.0%)
Vomiting	3 (2.0%)	1 (0.7%)	3 (2.0%)
Dental caries	3 (2.0%)	2 (1.4%)	2 (1.3%)
Gastrooesophageal reflux disease	2 (1.3%)	7 (4.7%)	2 (1.3%)
Abdominal pain upper	4 (2.7%)	3 (2.0%)	1 (0.7%)
Diarrhoea	6 (4.0%)	3 (2.0%)	0
Dyspepsia	0	3 (2.0%)	0
Skin and subcutaneous tissue disorders	14 (9.3%)	16 (10.8%)	17 (11.4%)
Rash	1 (0.7%)	2 (1.4%)	3 (2.0%)
Urticaria	3 (2.0%)	2 (1.4%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	27 (18.0%)	31 (20.9%)	23 (15.4%)
Back pain	10 (6.7%)	6 (4.1%)	8 (5.4%)
Arthralgia	2 (1.3%)	12 (8.1%)	7 (4.7%)
Myalgia	5 (3.3%)	3 (2.0%)	2 (1.3%)
Musculoskeletal pain	5 (3.3%)	0	0
General disorders and administration site conditions	29 (19.3%)	40 (27.0%)	28 (18.8%)
Injection site erythema	11 (7.3%)	10 (6.8%)	11 (7.4%)
Injection site reaction	3 (2.0%)	8 (5.4%)	5 (3.4%)
Injection site pain	4 (2.7%)	5 (3.4%)	3 (2.0%)
Fatigue	2 (1.3%)	3 (2.0%)	2 (1.3%)
Injection site bruising	2 (1.3%)	4 (2.7%)	2 (1.3%)
Injection site swelling	0	5 (3.4%)	2 (1.3%)
Pyrexia	1 (0.7%)	4 (2.7%)	2 (1.3%)
Chest pain	1 (0.7%)	5 (3.4%)	0
Oedema peripheral	3 (2.0%)	0	0
Injury, poisoning and procedural complications	23 (15.3%)	29 (19.6%)	19 (12.8%)
Accidental overdose	11 (7.3%)	12 (8.1%)	5 (3.4%)
Ligament sprain	2 (1.3%)	3 (2.0%)	2 (1.3%)
Fall	2 (1.3%)	4 (2.7%)	1 (0.7%)
Road traffic accident	1 (0.7%)	3 (2.0%)	1 (0.7%)
Intentional overdose	3 (2.0%)	0	0
Social circumstances	3 (2.0%)	0	0
Pregnancy of partner	3 (2.0%)	0	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one TEAE during the entire TEAE period
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group
Only PTs with at least one 2% in at least one group are presented

Treatment period adverse events leading to permanent treatment discontinuation

In the safety pool, the overall permanent treatment discontinuation rate due to treatment period AEs was lower in the dupilumab group compared to the placebo group (2.5% [11 patients] versus 5.3% [15 patients], respectively).

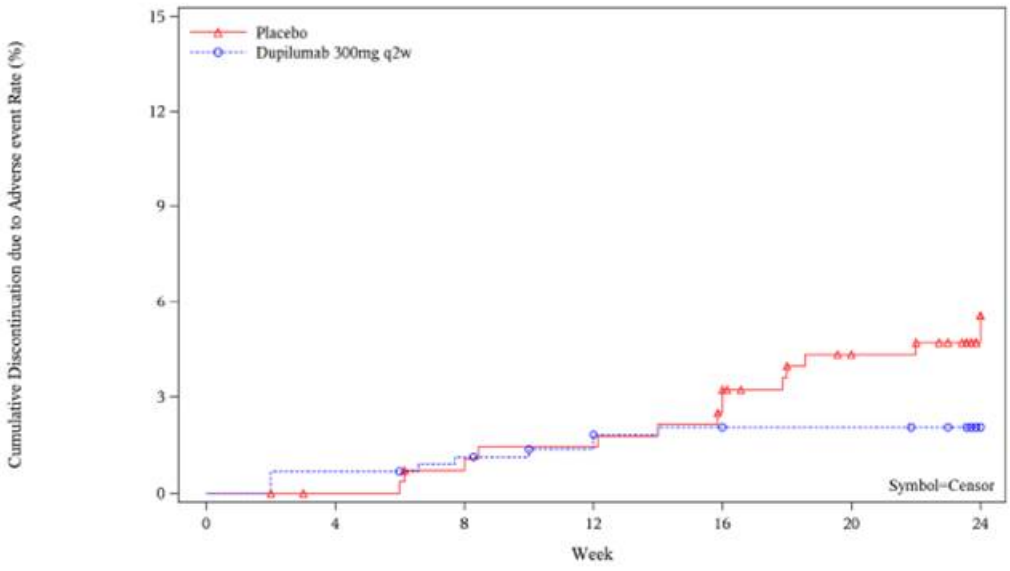
The most frequently reported AE that led to permanent treatment discontinuation in both treatment groups was nasal polyps (2 patients [0.5%] in the dupilumab group and 5 patients [1.8%] in the placebo group).
The remaining AEs leading to treatment discontinuation were singly reported and were distributed across a broad range of PTs without clustering to any particular SOC. One patient in each treatment group discontinued due to asthma (moderate in intensity).
Two patients in the dupilumab group reported more than one event that led to permanent treatment discontinuation.

One patient experienced 5 events (eosinophilia [severe and serious], arthralgia [severe], insomnia [mild], and 2 events of asthma [moderate]) and all were considered by the investigator to be related to IMP; the patient recovered from the events.
The other Patient experienced 2 events of nasal polyps; both were moderate in intensity and considered by the investigator to be not related to IMP. The patient recovered from the events.

Two patients in the placebo group reported more than one event that led to permanent treatment discontinuation. One patient experienced 4 events (nausea [mild], chills [mild], muscle spasms [moderate], and dizziness [moderate]). Chills and muscle spasms were considered by the investigator to be related to IMP and nausea and dizziness were not considered to be related to IMP. The patient recovered from all of the events. The other Patient experienced 2 events (palpitations [mild] and fatigue [moderate]) which were considered by the investigator to be related to IMP; the patient recovered from both events.

The majority of patients in the dupilumab and placebo treatment groups who permanently discontinued treatment due to a treatment period AE did so within the first 16 weeks of treatment: 81.8% (9 of 11 patients) for the dupilumab group compared with 73.3% (11 of 15 patients) in the placebo group. A Kaplan-Meier plot of time to treatment discontinuation due to an AE in the 24 week safety pool is provided below.

Number / Analysis: SAR231893 / OVERALL / ISS_NP_2018
Patient disposition
Overall patient disposition
Kaplan-Meier plot for time to treatment discontinuation due to an adverse event - 24 week pooled safety population



Number at Risk

Placebo	282	280	277	275	270	260	229
Dupilumab 300mg q2w	440	437	434	431	427	426	400

The number of subjects experiencing TEAEs leading to study drug discontinuation was in general low in the dupilumab treatment and placebo groups. The dupilumab treated group reached a plateau after week 15 and decreased during the following weeks. No special TEAE pattern which could have led to study drug discontinuation is discernible. The overall discontinuation rate was lower in the verum than in the placebo group (2.5% vs 5.3%).

Adverse events of special interest (AESI)

Adverse events of special interest and search criteria are listed in Table 3. An overview of the number (%) of patients who experienced treatment period AESIs or other selected AE grouping

events in the safety pool is presented in Table 28. The number of patients who experienced any treatment emergent AESIs in the safety pool was low and generally comparable across treatment groups during the treatment period.
Of the observed AESIs and other groupings of interest, serious/severe infections and epistaxis were more frequently seen in placebo-treated patients compared to dupilumab-treated patients. Injection site reactions, conjunctivitis (both broad/narrow CMQs), and eosinophilia CMQ were reported more frequently in dupilumab-treated patients than in placebo-treated patients. There were no cases reported for the following AESIs: anaphylactic reactions, symptomatic overdoses of IMP or non-investigational medicinal product, malignancy, or suicidal behavior.

Table 3 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries [SMQs] Version 20.0): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
Hypersensitivity (medically reviewed)	Hypersensitivity narrow SMQ (20000214) and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
Injection site reaction (serious/severe)	HLT = 'Injection site reaction' and [Serious='Y' or (Intensity='Severe' and lasting ≥ 24 hours)]
Infection (serious/severe)	Primary SOC = 'Infections and infestations' and (Intensity='Severe' or Serious='Y')
Parasitic infection	Infection Type 'Parasitic' checked on eCRF Infection Defined as AESI Complementary Form
Opportunistic infection	Infection Type 'Opportunistic' checked on eCRF Infection Defined as AESI Complementary Form
Potential drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Pregnancy	Primary SOC 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP/NIMP	Symptomatic Overdose is answered Yes, with Overdose of IMP and/or Overdose of NIMP answered Yes, on AE eCRF.
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	Sub-SMQ (20000091) – Malignant or unspecified tumors
Suicidal behavior	PT in (Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt)
Partner pregnancy	PT in (Pregnancy of partner, Miscarriage of partner)
Epistaxis/nose bleeding	PT = 'Epistaxis'
Conjunctivitis (narrow)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia)
Eosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

AE=adverse event, AESI=adverse event of special interest, eCRF=electronic case report form, HLT=high level term, IMP=investigational medicinal product, MedDRA= Medical Dictionary for Regulatory Activities, NIMP=non investigational medicinal product, PT=preferred term, SOC=system organ class, SMQ=Standardised MedDRA Query, Y=yes

The number (%) of patients experiencing a treatment period AE, SAE, and AE leading to permanent treatment discontinuation were summarized by AE category (AESI or other selected

Table 28 - Number (%) of patients with AESIs and other selected AE grouping events by category and PT - 24 week pooled safety population

Category Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
AESI	11 (3.9%)	12 (2.7%)
Anaphylactic reaction	0	0
Hypersensitivity (medically reviewed)	5 (1.8%)	5 (1.1%)
Dermatitis	2 (0.7%)	1 (0.2%)
Drug hypersensitivity	0	1 (0.2%)
Eosinophilic granulomatosis with polyangiitis[a]	0	1 (0.2%)
Exfoliative rash	0	1 (0.2%)
Rash macular	0	1 (0.2%)
Dermatitis allergic	1 (0.4%)	0
Dermatitis atopic	1 (0.4%)	0
Rash	1 (0.4%)	0
Injection site reaction (serious/severe)	0	1 (0.2%)
Injection site reaction	0	1 (0.2%)
Infection (serious/severe)	5 (1.8%)	4 (0.9%)
Appendicitis	0	1 (0.2%)
Cellulitis	0	1 (0.2%)
Diverticulitis	0	1 (0.2%)
Infectious pleural effusion	0	1 (0.2%)
Septic shock	0	1 (0.2%)
Erysipelas	1 (0.4%)	0
Pneumonia	1 (0.4%)	0
Sinusitis	1 (0.4%)	0
Tonsillitis	1 (0.4%)	0
Wound infection	1 (0.4%)	0
Parasitic infection	1 (0.4%)	0
Vulvovaginitis trichomonal	1 (0.4%)	0

Opportunistic infection	1 (0.4%)	0
Vulvovaginitis trichomonal	1 (0.4%)	0
Potential drug-related hepatic disorders	0	2 (0.5%)
Alanine aminotransferase increased	0	2 (0.5%)
Aspartate aminotransferase increased	0	1 (0.2%)
Pregnancy	1 (0.4%)	0
Pregnancy	1 (0.4%)	0
Symptomatic overdose	0	0
Other AE grouping event	56 (19.9%)	93 (21.1%)
Injection site reaction	34 (12.1%)	61 (13.9%)
Injection site erythema	22 (7.8%)	28 (6.4%)
Injection site reaction	5 (1.8%)	15 (3.4%)
Injection site pain	4 (1.4%)	8 (1.8%)
Injection site swelling	1 (0.4%)	6 (1.4%)
Injection site bruising	2 (0.7%)	5 (1.1%)
Injection site pruritus	0	3 (0.7%)
Injection site rash	0	3 (0.7%)
Injection site urticaria	1 (0.4%)	3 (0.7%)
Injection site warmth	0	2 (0.5%)
Injection site dermatitis	0	1 (0.2%)
Injection site exfoliation	0	1 (0.2%)
Injection site haematoma	2 (0.7%)	1 (0.2%)
Injection site haemorrhage	1 (0.4%)	1 (0.2%)
Injection site induration	0	1 (0.2%)
Injection site irritation	0	1 (0.2%)
Injection site nodule	0	1 (0.2%)
Injection site oedema	0	1 (0.2%)
Injection site discolouration	1 (0.4%)	0
Injection site hypersensitivity	1 (0.4%)	0
Injection site inflammation	1 (0.4%)	0
Malignancy	0	0
Suicidal behavior	0	0

Category Preferred Term n(%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
Partner pregnancy	2 (0.7%)	0
Miscarriage of partner	1 (0.4%)	0
Pregnancy of partner	2 (0.7%)	0
Epistaxis/nose bleeding	20 (7.1%)	25 (5.7%)
Epistaxis	20 (7.1%)	25 (5.7%)
Conjunctivitis (narrow)	1 (0.4%)	7 (1.6%)
Conjunctivitis	0	6 (1.4%)
Conjunctivitis bacterial	0	1 (0.2%)
Conjunctivitis allergic	1 (0.4%)	0
Conjunctivitis (broad)	1 (0.4%)	12 (2.7%)
Conjunctivitis	0	6 (1.4%)
Dry eye	0	2 (0.5%)
Blepharitis	0	1 (0.2%)
Conjunctival hyperaemia	0	1 (0.2%)
Conjunctivitis bacterial	0	1 (0.2%)
Eye discharge	0	1 (0.2%)
Conjunctivitis allergic	1 (0.4%)	0
Eosinophilia	1 (0.4%)	6 (1.4%)
Eosinophilia	1 (0.4%)	5 (1.1%)
Eosinophil count increased	0	1 (0.2%)
Eosinophilic granulomatosis with polyangiitis	0	1 (0.2%)

AESI: Adverse event of special interest, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one AESI/other AE grouping event
Note: Table sorted by AESI/other AE grouping category and decreasing percentage of PT in dupilumab 300 mg q2w group within category
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
a Upon medical review, this case was considered an auto-immune condition and not a classical immediate or delayed hypersensitivity reaction.
Source: PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_aesi_sum_s_t.sas
OUT=REPORT/OUTPUT/ae_aesi_sum_by24_s_t_i.rtf (12OCT2018 - 14:13)

Anaphylactic reaction/systemic hypersensitivity

Anaphylactic reaction

In the safety pool, no patient reported an anaphylactic reaction. Importantly, no patient reported an anaphylactic reaction at any time in Study EFC14146 or in Study EFC14280.

Potential systemic hypersensitivity reaction

In the safety pool, the proportion of patients who experienced potential systemic hypersensitivity events, which were medically reviewed, was similar in the dupilumab and placebo groups (1.1% [5 patients] and 1.8% [5 patients], respectively).

Of the 5 patients in the dupilumab group, 3 patients (0.7%) experienced events (all mild) coded under the skin and subcutaneous tissue disorders SOC (PTs of dermatitis, exfoliative rash, and rash macular). One patient discontinued treatment due to rash macular. One patient experienced a PT of drug hypersensitivity with diarrhea and facial rash (moderate intensity) leading to treatment discontinuation. Within the hypersensitivity narrow SMQ, one patient in the dupilumab group had an SAE of EGPA. Upon medical review, this case was considered an auto-immune condition and not a classical immediate or delayed hypersensitivity reaction.

Of the 5 patients in the placebo group, all of the events were coded under the Skin and subcutaneous tissue disorders SOC (PTs were dermatitis [n=2], dermatitis allergic, dermatitis atopic, and rash). The events were mild or moderate in intensity, were not SAEs, and did not result in permanent treatment discontinuation.

Injection site reactions

Injection site reactions (high level term)

Events of injection site reactions were collected as part of the safety program and serious or severe injection site reactions lasting 24 hours or longer were handled as AESIs in the dupilumab program.

In the safety pool, the proportion of patients who experienced injection site reactions, identified by HLT, was similar in the dupilumab and placebo groups (13.9% and 12.1%, respectively). The most frequently reported PT in both the dupilumab and placebo groups was injection site erythema (6.4% and 7.8%, respectively). Among patients who experienced injection site reactions, 1 dupilumab-treated patient had an event that was considered severe in intensity. None of the injection site reaction events were SAEs or led to permanent treatment discontinuation.
For the dupilumab group, 3.6% of patients developed injection site reactions at Week 0 which decreased to 2.1% at Week 12 and 1.0% at Week 24. For the placebo group, 2.8% of patients developed injection site reactions at Week 0 and remained at similar percentages at Week 12 (2.9%) and Week 24 (2.0%).

Serious Injection site reactions or severe injection site reactions that last 24 hours or more (AESI)
One patient (014280-620-0001-00209) in the dupilumab group, who was ADA-negative throughout the study, experienced a severe AE of injection site reaction that lasted 24 hours or more; it was considered to be treatment-related but did not lead to permanent treatment discontinuation. No patients in the placebo group reported a serious or severe injection site reaction that lasted 24 hours or more (Table 28).

Infection (serious/severe)
Analysis of severe/serious infection AESIs was based on events identified by the primary SOC 'Infections and infestations' and assessed as severe or serious by the investigator. The incidence of severe or serious infections was low in both treatment groups (0.9% [4 patients] in the dupilumab group and 1.8% [5 patients] in the placebo group). Most severe or serious infection PTs occurred in single patients within a treatment group and without any apparent pattern. None of the events led to permanent treatment discontinuation. In 3 dupilumab-treated patients, 3 infections were SAEs: diverticulitis, appendicitis, and infectious pleural effusion with septic shock due to esophageal perforation secondary to ingestion of a fishbone.

In 3 placebo-treated patients, 3 infections were SAEs: erysipelas, pneumonia, and wound infection.

Parasitic infection
One placebo-treated patient experienced a parasitic infection of vulvovaginitis trichomonal (Table 28). The infection was considered by the investigator to be mild in intensity and not related to IMP; the patient recovered. No parasitic infections were reported in dupilumab-treated patients in the safety pool or at any time in Study EFC14146 or in Study EFC14280.

Opportunistic infection
One placebo-treated patient experienced a parasitic infection of vulvovaginitis trichomonal which was considered by the investigator to be an opportunistic infection described in the paragraph above (Table 28).
No opportunistic infections were reported in dupilumab-treated patients in the safety pool or at any time in Study EFC14146 or in Study EFC14280.

Potential drug-related hepatic disorders
Two patients (both in the dupilumab group) experienced potential drug-related hepatic disorder AESIs during the treatment period. One patient had an event of ALT increased (>3 × ULN); values were 4.70 ULN (PCSA, 188 IU/L) on Day 113, 1.23 ULN (high) on Day 119, and 0.55 ULN on Day 166. The other patient had 2 events (ALT increased and AST increased (<3 × ULN, max 65 and 87 IU/L respectively) on Day 116; these 2 events were not PCSAs as they did not meet the criteria. These events were unrelated non-serious AEs and did not lead to permanent treatment discontinuation; both patients recovered during ongoing treatment with dupilumab without corrective treatment.

Pregnancy and partner pregnancy
No pregnancies or partner pregnancies were reported in the dupilumab group. In the placebo group, one patient reported a pregnancy. The IMP was discontinued after the third dose as a result of the pregnancy. The pregnancy ended in a live healthy birth.
Two placebo-treated patients reported partner pregnancies. For 1 patient's partner, the pregnancy ended in a spontaneous abortion. The other partner pregnancy was ongoing at the time of database lock (Table 28).

Symptomatic overdose
There were no cases of symptomatic overdose reported in dupilumab-treated patients or in placebo-treated patients in the safety pool (Table 28), or at any time in Study EFC14146 or in Study EFC14280.

Updated Safety evaluation submitted following request from CHMP with responses to the RSI.

In the time between the initial data cut-off (29 August 2018) and the end of the study (16 November 2018), a total of 29 newly reported treatment-emergent adverse events (TEAEs) in 21 patients in the placebo group, 42 newly reported TEAEs in 24 patients in the dupilumab 300 mg q2w-q4w group, and 29 newly reported TEAEs in 16 patients in the dupilumab 300 mg q2w group (see below). Most of these newly reported TEAEs occurred in patients who already reported TEAEs up to the initial cut-off date and that were described in the main CSR. During the additional follow-up period after the initial cut-off date, there were only 5 additional patients with no previously reported TEAE, who experienced at least 1 TEAE: 1 patient in the dupilumab 300 mg q2w group (asthma), 2 patients in the dupilumab 300 mg q2w-q4w group (rhinitis, nasal polyps, and pneumonia in 1 patient and anosmia in 1 patient), and 2 patients in the placebo group (nasal polyps for both).

Overview of adverse event profile: New treatment-emergent adverse events during the entire TEAE period reported after interim database lock - Safety population

		Dupilumab	
n(%)	Placebo (N=150)	300mg q2w-q4w (N=148)	300mg q2w (N=149)
Patients with any TEAE	21 (14.0%)	24 (16.2%)	16 (10.7%)
Patients with any treatment emergent SAE	0	2 (1.4%)	0
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	0

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event

n (%) = number and percentage of patients with at least one new TEAE during the entire TEAE period reported after interim database lock

No deaths occurred during the period between the previous data cut-off and the end of study. Two patients in the dupilumab 300 mg q2w-q4w group reported new treatment-emergent SAEs (acute renal injury and pyrexia; pneumonia) and 1 patient in the placebo group had a previously reported non-serious TEAE of nasal polyps, which was upgraded to SAE.

During the off-treatment follow-up period after the initial cut-off date for the main CSR, there were 9 newly reported treatment-emergent AESIs: 3 TEAEs of hypersensitivity (2 patients in the dupilumab 300 mg q2w group and 1 patient in the 300 mg q2w-q4w group), 4 additional cases of severe/serious infection (1 patient in the dupilumab 300 mg q2w group, 2 patients in the dupilumab 300 mg q2w-q4w group, and 1 patient in the placebo group), 1 case of opportunistic infection (peritonsillar abscess) in the placebo group, and 1 case of potentially drug-related hepatic disorders (dupilumab 300 mg q2w-q4w group). Among other selected adverse event (AE) groupings, 2 additional cases were reported: 1 case of injection site reaction that occurred during the time period for the main CSR but was reported after the cut-off date (dupilumab 300 mg q2w group) and 1 case of epistaxis (dupilumab 300 mg q2w-q4w group).

Other selected AE groupings

Malignancy
No malignancies were reported in dupilumab-treated patients or in placebo-treated patients in the safety pool (Table 28). One patient in the placebo group in Study EFC14146 (outside of the safety period) had an SAE of anal carcinoma that was not recovered/resolved by database lock. No malignancies were reported in dupilumab-treated patients at any time in Study EFC14146 or in Study EFC14280.

Suicidal behavior
No suicidal behaviors were reported in dupilumab-treated patients or in placebo-treated patients in the pooled safety population (Table 28). No patient reported suicidal behavior at any time in Study EFC14146 or in Study EFC14280.

Epistaxis/nose bleeding
In the safety pool, the incidence of epistaxis was lower in the dupilumab group compared with the placebo group (5.7% [25 patients] versus 7.1% [20 patients], respectively). None of the events were SAEs and none led to permanent treatment discontinuation.

Conjunctivitis (broad and narrow)
In the safety pool, the proportion of patients who experienced conjunctivitis based on the narrow CMQ (Table 3) was low (1.6% [7 patients] in the dupilumab group and 0.4% [1 patient] in the placebo group). The most frequently reported PT in the dupilumab group was conjunctivitis (6 patients). None of the events were serious or severe and none led to permanent treatment discontinuation.

In the safety pool, the proportion of patients who experienced conjunctivitis based on the broad CMQ was higher in the dupilumab group (2.7% [12 patients]) compared with the placebo group (0.4% [1 patient]).

The most frequently reported PT in the dupilumab group was conjunctivitis (6 patients [1.4%]) in the infections and infestations SOC. None of the events were SAEs and none led to permanent treatment discontinuation. Although 6.0%, 11.4%, and 59.1% of patients reported a history of AD, allergic conjunctivitis, or asthma respectively at baseline, there was no apparent association of conjunctivitis with history of these conditions. There was one patient in the dupilumab treatment group during the 24-week pooled treatment period with 2 episodes of uncomplicated mild conjunctivitis on Day 5 and Day 23 which were unrelated and did not lead to treatment discontinuation.

Eosinophilia
As a transient rise in blood eosinophils was seen in some dupilumab treated patients in the development program for AD and for asthma, the protocols for Phase 3 studies EFC14146 and EFC14280 specified that when a laboratory test revealed an eosinophil blood count >3.0 Giga/L during treatment, the investigator was required to report this finding as a TEAE, even if it was without any associated clinical symptom(s).

An analysis on a pre-specified grouping of eosinophilia TEAEs defined as eosinophilia CMQ was performed, including the HLT eosinophilic disorders (which includes the PTs of eosinophilia and EGPA), plus the PT eosinophil count increased.
In the safety pool, the incidence of eosinophilia CMQ was low but numerically higher in the dupilumab group (1.4% [6 patients]) compared with the placebo group (0.4% [1 patient]) (Table 36). Two TEAEs of eosinophilia were associated with clinical symptoms in dupilumab-treated patients. These 2 events were serious, severe, and led to permanent treatment discontinuation: (EGPA) and (eosinophilia).
Brief narratives for these 2 patients are provided below. In addition, there were 5 eosinophilia TEAEs (4 in the dupilumab group and 1 in the placebo group) which were isolated laboratory findings without any associated clinical symptoms. Four of these events (3 in the dupilumab group

and 1 in placebo) were considered mild or moderate in intensity, were self-limited and did not require corrective treatment or IMP interruption. The fifth case was considered severe and related to the IMP. It occurred in a dupilumab-treated patient who recovered from this event after temporary interruption of treatment and the event did not reoccur after resumption of treatment.

Across both studies through the treatment-emergent period, a total of 12 patients experienced TEAEs in the eosinophilia CMQ: 5 patients in Study EFC14146 (2 [1.5%] placebo, 3 [2.1%] dupilumab) and 7 patients (2 [1.3%] placebo, 5 [1.7%] dupilumab) in Study EFC14280 (Table 37). There was no imbalance between dupilumab and placebo in the occurrence of these eosinophilia TEAEs with or without clinical symptoms.

Table 37 - Summary of all patients with eosinophilia CMQ reported across both studies (EFC14146 and EFC14280)

Eosinophilia	Study EFC14280			Study EFC14146	
	Placebo (N=150)	Dupilumab 300 mg q2w-q4w (N=148)	Dupilumab 300 mg q2w (N=149)	Placebo (N=132)	Dupilumab 300 mg q2w (N=143)
Patients with any TEAE	2 (1.3%)	3 (2.0%)	2 (1.3%)	2 (1.5%)	3 (2.1%)
Primary System Organ Class/ Preferred Term n(%)					
Blood and lymphatic system disorders	1 (0.7%)	2 (1.4%)	2 (1.3%)	1 (0.8%)	2 (1.4%)
Eosinophilia	1 (0.7%)	2 (1.4%)	2 (1.3%)	1 (0.8%)	2 (1.4%)
Immune system disorders	0	1 (0.7%)[a]	0	1 (0.8%)	1 (0.7%)
Eosinophilic granulomatosis with polyangiitis	0	1 (0.7%)	0	1 (0.8%)	1 (0.7%)
Investigations	1 (0.7%)	0	0	0	1 (0.7%)
Eosinophil count increased	1 (0.7%)	0	0	0	1 (0.7%)

Source: 5.3.5.1 Study EFC14146 Appendix 16.2.7 AE data[16.2.7.11.34] and Study EFC14280 Appendix 16.2.7 AE data [16.2.7.7.38]

a Patient No. 014280-376-0001-00203 was randomized to the placebo group and received placebo throughout the treatment period with the exception of a single dose of dupilumab 300 mg that was inappropriately administered on Day 30, ie, more than 300 days prior to the episode of EGPA.

While there were 2 cases of eosinophilia with clinical symptoms in the safety pool, there were a total of 4 cases of eosinophilia with clinical symptoms observed across the treatment-emergent periods of both studies, all in patients with a history of asthma. All were SAEs: 2 dupilumab-treated patients with eosinophilia and EGPA in the 24-week safety pool period and 2 placebo-treated patients with EGPA outside of the 24-week safety pool period. One of these placebo-treated patients had been given a single dose of dupilumab more than 300 days before the onset of EGPA. An additional patient had a TEAE of eosinophilia associated with severe arthralgia.

Cardiovascular events (Studies EFC14146 and EFC14280 (all study periods))

Serious AEs in the cardiac disorders SOC, nervous system disorders SOC, vascular disorders SOC, with a PT of pulmonary embolism, and any event with an outcome of death, regardless of cause or timing, were submitted to the independent Cardiovascular Classification Process for a final assessment of the events.

Table 38 presents serious events that occurred at any time (ie, pre-treatment, on-treatment, and post-treatment) in Studies EFC14146 and EFC14280. A total of 10 serious cases were submitted for blinded cardiologist review of which 3 (0.7%) cases were in dupilumab-treated patients and 7 (2.5%) cases were in placebo-treated patients. None of the events were considered by the investigator to be related to IMP.

In placebo-treated patients, 4 of the 7 cases were assessed as CV events. The reported PTs were: acute myocardial infarction , peripheral arterial occlusive disease, syncope, and aortic valve stenosis. The other 3 cases were assessed as non-CV events: hypertension, lumbar radiculopathy and temporal lobe epilepsy.

In dupilumab-treated patients, 1 of the 3 cases was assessed as a CV event. The reported PT was acute myocardial infarction, which was nonfatal. The other 2 cases were assessed as non-CV events: traumatic intracranial haemorrhage [dupilumab 300 mg q2w-q4w]) and carpal tunnel syndrome.

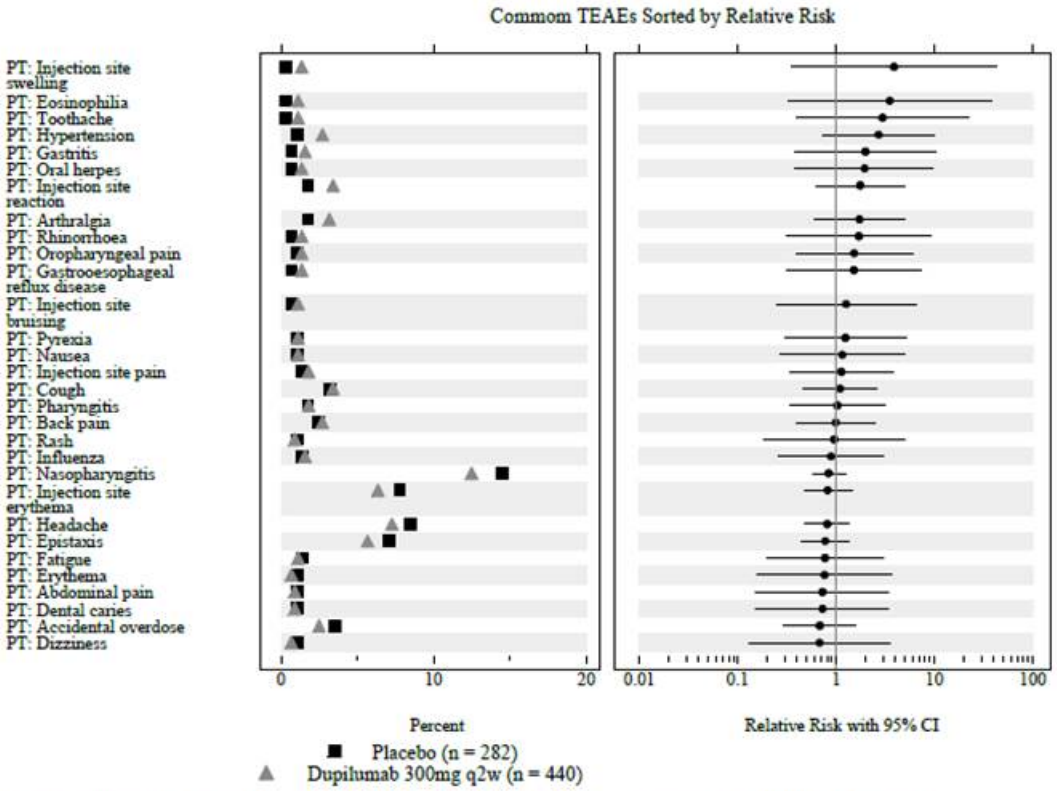
The only events categorized as MACE were the 2 myocardial infarctions. Two of the 10 serious cases were fatal of which one was assessed as a CV death [placebo]; acute myocardial infarction and one was assessed as a non-CV death [dupilumab 300 mg q2w-q4w]; traumatic intracranial haemorrhage. These 2 cases are presented in Section (Deaths).

Adverse Drug Reactions

The primary assessment for ADRs was conducted in the 24-week safety pool (Studies EFC14146 and EFC14280). Analysis was based on individual PTs and selected AE groupings (predefined SMQs/CMQs) in the pooled 24-week safety population (N=722 subjects).

The threshold for TEAEs selection was based on ≥1% incidence in the dupilumab group and ≥1% difference versus placebo.

ADRs were identified from PTs that had a lower bound of the 95% CI of relative risk >1 compared to placebo. These ADRs were then selected for fatal outcome, seriousness and severity criteria, followed by impact on IMP administration (ie, resulted in treatment discontinuation).
As shown in Figure 2, none of the PTs met the ADR criteria (≥1% incidence with ≥1% difference and lower bound of the 95% CI of relative risk >1) suggesting no quantitative difference from placebo. Similarly, no events fulfilled the qualitative criteria for ADR in the dupilumab group based on medical judgement of causality. As noted, no new ADRs were identified in the CRSwNP program using these criteria. Amongst
ADRs observed in dupilumab-treated patients in the AD and/or asthma programs, injection site reactions and conjunctivitis are considered ADRs in the CRSwNP program. In the CRSwNP program, these events also demonstrated an imbalance in the dupilumab group(s) compared to the placebo group, though the rate of these ADRs was lower as compared with the other dupilumab clinical programs.



Confidence intervals are calculated using Cochran-Mantel-Haenszel approach, stratified by study.
Source: PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/ae_forest_s_g.sas
OUT=REPORT/OUTPUT/ae_forest_freq1_by24_s_g_x.rtf (19OCT2018 - 9:09)

Injection site reactions were observed more frequently in the dupilumab group versus placebo, with the PTs of injection site reaction and injection site swelling meeting the criteria of ≥1% incidence and ≥1% difference versus placebo. Injection site reactions associated with injectable therapeutics are unlikely to be disease-specific. Therefore, given the existing ADRs of injection site reactions in the asthma and AD programs, these 2 PTs are selected as ADRs in the CRSwNP program.

Similarly, conjunctivitis (narrow and broad CMQs) was observed more frequently in the dupilumab group versus placebo, with PT of conjunctivitis meeting the criteria of ≥1% incidence and ≥1% difference versus placebo. None of the events of conjunctivitis were severe or serious, or required permanent treatment discontinuation. All recovered on topical treatment or antibiotics. Overall incidence of conjunctivitis is similar to what was seen in asthma (albeit the placebo incidence being higher than dupilumab in the asthma program) and less than that observed in AD. In light of the fact that conjunctivitis had previously been identified as an ADR in the AD program and in the absence of an alternative etiology, this PT is selected as an ADR in the CRSwNP program.

In the safety pool, an imbalance was observed for the eosinophilia CMQ, which was primarily driven by a protocol-specified requirement to report these AEs in the setting of a laboratory abnormality regardless of demonstrated clinical symptoms. As discussed in sections above, the vast majority of these eosinophilia TEAEs were not symptomatic and suffered no clinical consequences. While there were 2 cases of eosinophilia with clinical symptoms in dupilumab-treated patients in the safety pool, there were no differences across the complete treatment-emergent periods of both studies, in either symptomatic or asymptomatic eosinophilia TEAEs in patients treated with dupilumab compared to placebo. Therefore, eosinophilia is not considered an ADR with dupilumab in the CRSwNP program.

In the safety pool and through the complete treatment-emergent periods of the two Phase 3 studies, there was no imbalance in hypersensitivity reactions in the CRSwNP program and no anaphylaxis reactions or serum sickness cases were reported. Dupilumab therapy in patients with

CRSwNP was not associated with increased risks of infections (bacterial, viral, opportunistic, or parasitic), malignancies, or hepatobiliary disorders. Serious CV cases were rare and not imbalanced after dupilumab treatment as compared with placebo in the CRSwNP studies. The incidence of herpes viral infection, eosinophilic disorders/eosinophil count increased, hepatobiliary disorders, and cardiac disorders was similar or less than that observed in dupilumab-treated patients within the safety pools for the asthma and AD programs. There were no rare events that met the criteria for ADR. Based on the above, the ADRs for the dupilumab-treated patients in the CRSwNP program are provided in Table 39.

Table 39 - Adverse drug reactions in dupilumab-treated patients in the 24-week safety pool (studies EFC14146 and EFC14280)

Adverse Drug Reaction by preferred term	Dupilumab 300 mg Q2W N=440 n (%)	Placebo N=282 n (%)
Injection site reaction	15 (3.4%)	5 (1.8%)
Injection site swelling	6 (1.4%)	1 (0.4%)
Conjunctivitis	6 (1.4%)	0 (0%)

Source: 5.3.5.3 ISS, Appendix 1.4.1.5.

Looking at the ADRs for CRSwNP in the 52-week Study EFC14280, conjunctivitis was reported in 1.7% (5/297), injection site reaction in 4.4% (13/297), and injection site swelling in 2.4% (7/297) of patients in the dupilumab groups versus 0.7% (1/150), 2.0% (3/150), and 0% of patients in the placebo group, respectively.

b) Study ACT12340

Adverse events

Treatment-emergent AEs were reported for 55 patients in total; 30 (100%) patients in the dupilumab group and 25 (83.3%) in the placebo group. Most TEAEs were mild or moderate in intensity and resolved by the end-of-study. No deaths were reported during the treatment period; one patient died during the screening period (before receiving IMP). Permanent treatment discontinuation of study drug due to a TEAE was reported by 7 patients in total, of these, 5 were placebo patients.

The most frequently reported PTs in the dupilumab group included nasopharyngitis (46.7%), injection site reaction (40.0%), epistaxis (23.3%), orophayngeal pain (23.3%), headache (20.0%), upper respiratory tract infection (13.3%), dizziness (10.0%), and back pain (10.0%), while the most frequently reported PTs in the placebo group included nasopharyngitis (33.3%), headache (16.7%), bronchitis (13.3%), nasal polyps (10.0%), upper airway cough syndrome (10.0%), and asthma (10.0%) (Table 10).

A total of 14 patients reported any injection site reaction; 2 (6.7%) in the placebo group and 12 (40.0%) in the dupilumab group. One patient in the dupilumab group discontinued from the study due to a moderate injection site reaction. Injection site reaction in this patient recovered 5 days after the onset of the event without any corrective treatment. Overall, injection site erythema was the most frequently reported sign/symptom, followed by injection site pain.

Four patients in the dupilumab 300 mg treatment group had ≥4 episodes of injection site reactions compared to none in the placebo group. Imbalances for epistaxis and oropharyngeal pain were also observed in this study, 7 patients (23.3%) in the dupilumab group compared with 2 (6.7%) patients in the placebo group for both PTs (Table 10).

Table 10 - Number (%) of patients with common TEAEs, PT ≥ 5% in any treatment group, by primary SOC and PT in study ACT12340 – safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=30)	Dupilumab 300 mg qw (N=30)
Any Class	25 (83.3%)	30 (100%)
Infections and infestations	18 (60.0%)	23 (76.7%)
Nasopharyngitis	10 (33.3%)	14 (46.7%)
Upper respiratory tract infection	0	4 (13.3%)
Sinusitis	1 (3.3%)	2 (6.7%)
Bronchitis	4 (13.3%)	1 (3.3%)
Nervous system disorders	6 (20.0%)	12 (40.0%)
Headache	5 (16.7%)	6 (20.0%)
Dizziness	1 (3.3%)	3 (10.0%)
Sinus headache	1 (3.3%)	2 (6.7%)
Respiratory, thoracic and mediastinal disorders	10 (33.3%)	15 (50.0%)
Epistaxis	2 (6.7%)	7 (23.3%)
Oropharyngeal pain	2 (6.7%)	7 (23.3%)
Asthma	3 (10.0%)	2 (6.7%)
Cough	1 (3.3%)	2 (6.7%)
Rhinalgia	0	2 (6.7%)
Rhinitis allergic	0	2 (6.7%)
Nasal polyps	3 (10.0%)	1 (3.3%)
Upper-airway cough syndrome	3 (10.0%)	0
Gastrointestinal disorders	7 (23.3%)	6 (20.0%)
Abdominal pain	2 (6.7%)	0
Musculoskeletal and connective tissue disorders	1 (3.3%)	8 (26.7%)
Back pain	0	3 (10.0%)
Arthralgia	1 (3.3%)	2 (6.7%)
General disorders and administration site conditions	2 (6.7%)	13 (43.3%)
Injection site reaction	2 (6.7%)	12 (40.0%)
Investigations	3 (10.0%)	0
Blood creatine phosphokinase increased	2 (6.7%)	0
Vascular disorders	3 (10.0%)	0
Hypertension	2 (6.7%)	0

PT=preferred term; mg=milligram; N=number; qw=every week (weekly); SOC=system organ class; TEAE=treatment-emergent adverse event
MedDRA 17.1
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg group
Source: data extracted from the original marketing application for AD, 5.3.5.1 Study ACT12340, Table 42

Serious adverse events

A total of 6 patients experienced SAEs: 2 in the dupilumab group and 4 in the placebo group. Of the 2 patients in the dupilumab group who experienced SAEs, 1 patient reported an SAE of herpes zoster (located at the right upper arm) that was also considered an AESI and the other patient reported SAEs of arrhythmia, pain in extremity, hypoaesthesia, and mononeuropathy. The placebo patients reported SAEs of nasal polyps, uterine cancer, transient ischemic attack, and asthma (verbatim term [asthma exacerbation]). All treatment-emergent SAEs were assessed as not related to the study drug by the investigator.

Adverse events leading to permanent treatment discontinuation

Withdrawal of study treatment due to a TEAE was reported for relatively few patients (n=7;2 patients in the dupilumab group and 5 patients in the placebo group). Among those, 1 patient in the dupilumab group reported a severe drug-related TEAE (constipation) and 1 patient in the dupilumab group reported a moderate drug-related TEAE (injection site reaction). Two patients in the placebo group reported TEAEs of asthma (1 event was a serious event). Discontinuation of study treatment for 1 placebo-treated patient was due to several TEAEs (hypertension, headache, abdominal pain, and bronchitis) with 3 out of those 4 that resolved with corrective treatment. Other reasons for permanent drug discontinuation in the placebo group were hypersensitivity (n=1) and otitis media (n=1).

Adverse events of special interest
In this study, the prespecified AESIs were anaphylactic or acute allergic reactions requiring immediate treatment, severe injection site reactions that lasted for >24 hours, severe/serious infections (including opportunistic and parasitic infections), significant alanine aminotransferase (ALT) elevations, pregnancy, and symptomatic overdose. Only 1 AESI was reported and it was in the category of serious/severe infection (PT of herpes zoster); the case is described below.
• One 53-year-old male patient in the dupilumab group experienced an SAE of herpes zoster located at the right upper arm on Study Day 80. The event of herpes zoster was considered medically significant and an AESI. The patient was treated with valacyclovir and flupentixol dihydrochloride/melitracen hydrochloride. No action was taken with the IMP. On Study Day 153, the patient's herpes zoster resolved. The event herpes zoster was considered as not related to the study treatment by the investigator.

Eosinophilic TEAEs
No TEAEs of eosinophilia or blood eosinophil count increases were reported.

Clinical laboratory evaluations
For laboratory results, there was no reporting of serious and/or related hematological or biochemical disorders. PCSAs were observed in both treatment groups for increased eosinophils (>0.5 Giga/L or >ULN
[if ULN is ≥0.5 Giga/L]); the incidence was higher in the dupilumab group (43.3% [13/30]) compared with the placebo group (34.5% [10/29]).

Vital signs
No clinically meaningful differences between the placebo and dupilumab groups were observed in vital sign parameters (SBP, DBP, and HR). One patient in the placebo group had a PCSA in supine SBP of ≥160 mmHg and an increase from baseline of ≥20 mmHg. There were no reports of hypotension; however, hypertension was reported for 2 patients in the placebo group that presented moderate and mild cases respectively. For both patients, the TEAE was not assessed as drug-related or serious.

ECGs
No clinically meaningful differences between the placebo and dupilumab groups were observed in ECG parameters (HR, PR, QRS, QTc Bazett, and QTc Fridericia). No patient reported a QTc Bazett or Fridericia ≥500 ms.

Immunogenicity
Four patients exposed to dupilumab were ADA positive during the study. No ADA-positive patients experienced a hypersensitivity reaction during the study. The 4 ADA-positive patients experienced non-allergic local injection reaction (erythema, pain, edema and injection site stinging). Due to limited number of patients, no safety correlation can be made between ADA positive and negative patients in this study.

Safety conclusions
Dupilumab 300 mg qw was generally well-tolerated over 16 weeks of treatment in patients with CRSwNP. The safety results did not show any relevant differences between the placebo group and the dupilumab group except for a higher incidence of epistaxis and injection site reactions in dupilumab-treated patients. No safety signal was raised during the study.

Laboratory findings

a) safety pool studies EFC14146 and EFC14280

HEMATOLOGY
Red blood cells and platelets

Descriptive statistics
No relevant mean changes from baseline were observed for hematology parameters (hemoglobin, hematocrit, RBCs, and platelets) in the dupilumab and placebo treatment groups during the treatment period in the safety pool.

The percentage of patients with potentially clinically relevant abnormalities (PCSAs) for RBCs and platelets during the treatment period was low and comparable in both treatment groups. No patients had PCSAs for RBCs and platelets that were considered SAEs or were AEs that led to treatment discontinuation during the treatment period.

White blood cells
Descriptive statistics
No relevant mean changes from baseline were observed for WBC parameters (WBC count, neutrophils, lymphocytes, monocytes, and basophils) in the dupilumab and placebo treatment groups during the treatment period in the safety pool.

PCSA analysis
The number of patients with PCSAs for WBCs and WBC differential counts was balanced between treatment groups during the treatment period except for increased eosinophils that was more frequently observed in the combined dupilumab group compared to placebo. The most frequently reported PCSA in both treatment groups was for increased eosinophils (>0.5 Giga/L or >ULN [if ULN is ≥0.5 Giga/L]); incidence was higher in the dupilumab group (25.3%) compared with the placebo group (13.7%). Two dupilumab-treated patients in the safety pool experienced SAEs of eosinophilia: PT of eosinophilia and PT of EGPA.

Table 44 - White blood cell count: Number (%) of patients with abnormalities (PCSA) during the treatment period - 24 week pooled safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=282)	Dupilumab 300mg q2w (N=440)
WBC		
< 3.0 Giga/L (Non-Black); < 2.0 Giga/L (Black)	1/277 (0.4%)	1/427 (0.2%)
≥ 16.0 Giga/L	2/277 (0.7%)	3/427 (0.7%)
Lymphocytes		
> 4.0 Giga/L	5/277 (1.8%)	10/427 (2.3%)
Neutrophils		
< 1.5 Giga/L (Non-Black); < 1.0 Giga/L (Black)	6/277 (2.2%)	9/427 (2.1%)
Monocytes		
> 0.7 Giga/L	35/277 (12.6%)	31/427 (7.3%)
Basophils		
> 0.1 Giga/L	4/277 (1.4%)	4/427 (0.9%)
Eosinophils		
> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	38/277 (13.7%)	108/427 (25.3%)

PCSA: Potentially clinically significant abnormalities
The number (n) represents the subset of the total number of patients who met the criterion at least once during the treatment period. The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the treatment period.
For PCSA based on change from baseline, the denominator is restricted to patients having (non missing) baseline and a post-baseline value during the treatment period.
PGM=PRODOPS/SAR.231893/OVERALL/ISS_NP_2018/REPORT/PGM/lab_pcsa_s_t.sas
OUT=REPORT/OUTPUT/lab_pcsa_wbc_by24_s_t_i.rtf (12OCT2018 - 11:58)

Special assessment of blood eosinophils
In the safety pool, a transient increase in the mean blood eosinophil count was observed at Week 16 in the dupilumab group (0.147 Giga/L) versus no change in the placebo group (-0.007 Giga/L); with values returning to baseline values at Week 24. The median percent blood eosinophil count remained relatively unchanged for both dupilumab and placebo groups throughout the treatment period (Figure 3), indicating that the observed increase in mean was likely driven by a subset of

patients; median eosinophil changes from baseline at Week 16 were 0.05 Giga/L versus 0 Giga/L in the 2 groups, respectively.

The distribution of the maximum values of blood eosinophils during the 24-week treatment period by treatment group was analysed. The highest value in the dupilumab group was 8.55 Giga/L (distribution ranged from 0 Giga/L to 8.55 Giga/L) and the highest value in the placebo group was 2.97 Giga/L (distribution ranged from 0.01 Giga/L to 2.97 Giga/L). Patients with the 2 highest values in the dupilumab group were previously described cases of EGPA and eosinophilia with arthralgia, asthma, and insomnia. The third highest value in the dupilumab group was in a patient with asymptomatic eosinophilia.

For patients with baseline blood eosinophil counts <0.5 Giga/L, more patients in the dupilumab group (80 of 296 patients, 27.0%) than in the placebo group (42 of 188 patients, 22.3%) had post-baseline eosinophil counts increased to ≥0.5 Giga/L and <1 Giga/L. Similarly, more patients in the dupilumab group (21 of 296 patients, 7.1%) than in the placebo group (3 of 188 patients, 1.6%) had post-baseline eosinophil counts increased to ≥1 Giga/L and <1.5 Giga/L. No post-baseline eosinophil counts increased to ≥3 Giga/L were observed in either group.
A similar trend was also observed for patients with baseline eosinophil counts ≥0.5 Giga/L and <1 Giga/L, and ≥1 Giga/L and <1.5 Giga/L). More patients in the dupilumab group (12.6% and 21.1%) than in the placebo group (1.4% and 20.0%) had post-baseline peak eosinophil counts ≥1.5 Giga/L and <3 Giga/L. The analysis for patients with baseline eosinophils value of ≥1.5 Giga/L and <3 Giga/L was not conclusive due to the small number of patients in this category. In both studies, the median percent increases from baseline in blood eosinophil count was similar in the dupilumab and placebo groups.

CLINICAL CHEMISTRY

Metabolic parameters

Descriptive statistics

No relevant mean changes from baseline were observed for metabolic parameters (total cholesterol, total protein, albumin, and creatine kinase) in the dupilumab and placebo treatment groups during the treatment period in the safety.

PCSA analysis

The proportion of patients with PCSAs for metabolic parameters was balanced between treatment groups. The most frequently reported PCSA in both treatment groups was for high glucose levels (US units: ≥200 mg/dL [unfasted]; ≥126 mg/dL [fasted]); incidence was comparable in the dupilumab and placebo groups (5.6% and 4.7%, respectively). No patients had PCSAs for metabolic parameters that were considered SAEs or were AEs that led to permanent treatment discontinuation during the treatment period.

Electrolytes

Descriptive statistics

No relevant mean changes from baseline were observed for electrolytes (sodium, potassium, chloride, or bicarbonate) in the dupilumab and placebo treatment groups during the treatment period in the safety pool.

PCSA analysis

No patients in either treatment group had PCSAs for sodium or chloride during the treatment period. For PCSAs of increased potassium (≥5.5 mmol/L), incidence was 1.2% in the dupilumab group and 2.2% in the placebo group. No patients had PCSAs for electrolytes that were considered SAEs or were AEs that led to permanent treatment discontinuation during the treatment period.

Renal function parameters

Descriptive statistics

No relevant mean changes from baseline were observed for renal function parameters (creatinine, estimated creatinine clearance, uric acid, and BUN) in the dupilumab and placebo treatment groups during the treatment period in the safety pool.

PCSA analysis
The proportion of patients with PCSAs for renal function parameters was generally comparable between treatment groups. The most frequently reported PCSAs in both treatment groups was increased uric acid (US unit: ≥7 mg/dL); incidence was similar in the dupilumab and placebo groups (21.7% and 23.3%, respectively). For decreased creatinine clearance (mild, ≥60 - < 90 mL/min), incidence of PCSAs was similar in the dupilumab and placebo groups (16.9% and 16.8%, respectively).
Two placebo-treated patients had a severe decrease from baseline in GFR (≥15 - < 30 mL/min) versus no dupilumab-treated patients. No patients had PCSAs for renal function parameters that were considered SAEs or AEs that led to treatment discontinuation during the treatment period.

Liver function parameters
Descriptive statistics
No relevant mean changes from baseline were observed for liver function parameters (ALT, AST, ALP, LDH and total bilirubin) in the dupilumab and placebo treatment groups during the treatment period in the safety pool.

PCSA analysis
No patients had PCSAs for AST or alkaline phosphatase during the treatment period. One patient (0.2%) in the dupilumab group had ALT values >3 x ULN compared with 2 patients (0.7%) in the placebo group. For total bilirubin, 3 patients (0.7%) in the dupilumab group had at least one value >1.5 x ULN compared with 3 patients (1.1%) in the placebo group. One patient (0.4%) in the placebo group had a total bilirubin value >2 x ULN compared with no patients in the dupilumab group. The incidence of lactate dehydrogenase <LLN was similar in the dupilumab and placebo groups (8.3% and 7.2%, respectively).
No patients had PCSAs for liver function parameters that were considered SAEs or AEs that led to permanent treatment discontinuation during the treatment period. No patient had an ALT value >3 x ULN with a total bilirubin value > 2 x ULN. Thus, no Hy's Law cases were identified in the safety pool.

Vital Signs, Physical Examination and Other Observations related to Safety

Vital signs in the safety pool (EFC14146 and EFC14280)
Descriptive statistics
No relevant mean changes from baseline were observed for vital sign parameters (SBP, DBP, HR, weight, respiratory rate, and body temperature) in the dupilumab and placebo treatment groups during the treatment period in the safety pool. At baseline, the mean weight of placebo patients was higher than for dupilumab patients: 81.18 kg versus 80.33 kg, respectively. At Week 24, mean weights were increased in both treatment groups, more so in the dupliumab group (81.17 kg) though still lower than placebo (81.72 kg).

PCSA analysis
The proportion of patients with PCSAs for SBP and DBP was generally low and balanced between the treatment groups during the treatment period. The most frequently reported PCSA was weight increased (≥5% increase from baseline) with a higher incidence in the dupilumab group (13.5% [59 patients]) compared with the placebo group (8.9% [25 patients]). Incidence of weight decreased (≥5% decrease from baseline) was lower in the dupilumab group (3.0% [13 patients]) compared with the placebo group (7.5% [21 patients]). One patient (014280-792-0007-00206) in the placebo group experienced an SAE of weight decreased. This SAE did not result in permanent treatment discontinuation.

ECG parameters (EFC14146 and EFC14280)
ECG data for Studies EFC14146 and EFC14280 were not pooled, but reported in each separate study CSR. The number of patients with an abnormal ECG was well balanced between the treatment groups (see below).

Project Code / Study Number / Analysis: SAR231893 / EFC14146 / CSR
16.2.7 Other safety observations
16.2.7.7 ECG
16.2.7.7.1 ECG - Number (%) of patients with abnormalities during the entire TEAE period according to baseline status - Safety population

ECG Baseline Status n/N1 (%)	Placebo (N=132)	Dupilumab 300mg q2w (N=143)
ECG		
Total*		
Normal/Missing	118/128 (92.2%)	126/142 (88.7%)
Abnormal	10/128 (7.8%)	16/142 (11.3%)
Normal/Missing		
Normal/Missing	110/117 (94.0%)	116/122 (95.1%)
Abnormal	7/117 (6.0%)	6/122 (4.9%)

*Regardless of baseline status
Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline status.
PGM=PRODOPS/SAR231893/EFC14146/CSR/REPORT/PGM/ovs_ecg_s_t.sas OUT=REPORT/OUTPUT/ovs_ecg_s_t_n.rtf (10OCT2018 - 7:06)

Immunogenicity

Incidence and characterization of Anti-Dupilumab Antibodies

Anti dupilumab antibody status was determined at baseline (Day 1) and at prespecified time points. ADA population consisted of all patients in the safety population who received any study drug and who had at least one non-missing reportable ADA result post first dose. The definitions of ADA positive and negative patients are provided are as follows:

• **ADA positive patients** = Patients with Treatment-emergent or Treatment-boosted response
• **ADA negative patients** = Patients with Pre-existing immunoreactivity or negative in the ADA assay at all time points

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab and to those of other products may be misleading.

Dupilumab immunogenicity was evaluated in all dupilumab clinical studies.
Given the different measurement time points and limited patient numbers in Study ACT12340, a summary of ADA, and NAb incidence for CRSwNP patients is provided for Studies EFC14146 and EFC14280 only and pooled in Table 15.

The pool of dupilumab 300 mg q2w arms in Studies EFC14146 and EFC14280 is the principal source of data to evaluate ADA responses in patients with CRSwNP with the same treatment duration (24 weeks) and enables an adequate evaluation of persistent ADA responses.
The incidence of treatment-emergent ADA was 4.3% in the 300 mg q2w group compared to 2.1% in the placebo group (Table 15). Persistent ADA response was observed in 1.6% of all patients at 300 mg q2w compared to 0.7% for placebo. Most of these treatment emergent ADA responses were low titer. High titer ADA response (>10 000) was observed in 0.9% of patients treated with dupilumab and was not observed in patients on placebo. Approximately 2.5% of all patients at 300 mg q2w were classified as neutralizing antibody (NAb) positive compared to 0.7% in theplacebo group (Table 15).

Table 15 - ADA incidence in Phase 3 studies in patients with CRSwNP (Studies EFC14146 and EFC14280)

Anti-dupilumab antibodies N (%)	Pooled (24-week duration)[h]		Study EFC14280 (52-week TEAE period)[h]			Study EFC14146 (24-week TEAE period)[h]	
	Placebo (N=281)	300 mg q2w (N=438)	Placebo (N=149)	300 mg q2w–q4w (N=148)	300 mg q2w (N=148)	Placebo (N=132)	300 mg q2w (N=143)
Pre-existing ADA[a]	6 (2.1%)	9 (2.1%)	4 (2.7%)	4 (2.7%)	4 (2.7%)	2 (1.5%)	1 (0.7%)
Treatment-emergent response[b]	6 (2.1%)	19 (4.3%)	6 (4.0%)	12 (8.1%)	8 (5.4%)	7 (5.3%)	22 (15.4%)
Persistent response[c]	2 (0.7%)	7 (1.6%)	1 (0.7%)	5 (3.4%)	3 (2.0%)	2 (1.5%)	5 (3.5%)
Indeterminate response[d]	2 (0.7%)	5 (1.1%)	2 (1.3%)	4 (2.7%)	2 (1.4%)	1 (0.8%)	8 (5.6%)
Transient response[e]	2 (0.7%)	7 (1.6%)	3 (2.0%)	3 (2.0%)	3 (2.0%)	4 (3.0%)	9 (6.3%)
Peak post-baseline titer							
Low (<1,000)	5 (1.8%)	15 (3.4%)	4 (2.7%)	11 (7.4%)[i]	6 (4.1%)	7 (5.3%)	20 (14.0%)
Moderate (1,000-10,000)	1 (0.4%)	0	2 (1.3%)	0	0	0	1 (0.7%)
High (>10,000)	0	4 (0.9%)[g]	0	1 (0.7%)	2 (1.4%)	0	1 (0.7%)[g]
Treatment-boosted response[f]	1 (0.4%)	0	1 (0.7%)	0	0	0	0
Neutralizing antibodies	2 (0.7%)	11 (2.5%)	3 (2.0%)	9 (6.1%)	5 (3.4%)	0	15 (10.5%)

a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.

b A positive response in the ADA assay post first dose when baseline results are negative or missing.

c Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.

d Treatment-emergent response with only the last collected sample positive in the ADA assay.

e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.

f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

g Includes one patient with high titer ADA in the placebo group who was administered one dose of dupilumab

h Includes 24 weeks follow-up for Study EFC14146 and limited number patients with 12 weeks follow-up for Study EFC14280) and the no follow-up period Pooled 24-week treatment pool

i Includes one patient with low titer ADA in the placebo group who was administered one dose of dupilumab

Source: 5.3.5.1 Studies EFC14146 and EFC14280, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.1.2.2] and [16.2.5.4.1.2.6]

The treatment-emergent ADA incidence was similar (2.1 to 4.8%) following dupilumab treatment for 24 weeks (300 mg q2w in Study EFC14146) or 52 weeks (300 mg q2w and 300 mg q2−q4w in Study EFC14280) as well as placebo treatment (0.7% to 4.8% in Studies EFC14146 and EFC14280). However, the proportion of patients with a treatment-emergent ADA positive response in the post-treatment period varied depending on the follow-up duration (13.7% for 300 mg q2w with 24-week follow-up in Study EFC14146 versus 2.4% for 12-week follow-up in Study EFC14280) and dose regimen (14.3% for 300 mg q2w-q4w versus 2.4% for 300 mg q2w in Study EFC14280). It is to be noted that the 24-week treatment pool does not include a follow-up period, while a 12 to 24-week follow-up duration is included in the TEAE period for Studies EFC14146 and EFC14280, which explains the apparent numerical difference of treatment-emergent ADA incidence between the pool and the individual studies in Table 15.

As shown in Table 16, 5.4% of patients with CRSwNP who received dupilumab 300 mg q2w for 52 weeks developed antibodies to dupilumab; 2.0% exhibited persistent ADA responses, and 3.4% had neutralizing antibodies. A total of 4.0% of patients in the placebo group in the 52-week study were positive for antibodies to dupilumab; 0.7% exhibited persistent ADA response and 2.0% had neutralizing antibodies. The ADA incidence was similar across the CRSwNP, AD, and asthma populations with respect to treatment emergent positive ADA response (5-6%), persistent ADA response (~2%), and neutralizing antibody response (1-3%) after 52 weeks of treatment at 300 mg q2w. The combined ADA and NAb incidence in patients with CRSwNP, AD, and asthma is presented in Table 16.

Table 16 - ADA incidence in patients with CRSwNP, asthma and AD in 52-week studies (EFC14280, EFC13579 and AD-1224)

Anti-dupilumab antibodies N (%)	Study EFC14280 (CRSwNP)		Study EFC13579 (Asthma)		Study AD-1224 (AD)		Combined CRSwNP, asthma and AD	
	Placebo (N=149)	300 mg q2w (N=148)	Placebo[g] (N=630)	300 mg q2w (N=626)	Placebo (N=305)	300 mg q2w (N=105)	All Placebo[h] (N=1084)	300 mg q2w (N=879)
Pre-existing ADA[a]	4 (2.7%)	4 (2.7%)	7 (1.1%)	9 (1.4%)	18 (5.9%)	3 (2.9%)	29 (2.7%)	16 (1.8%)
Treatment-emergent response[b]	6 (4.0%)	8 (5.4%)	22 (3.5%)	32 (5.1%)	20 (6.6%)	6 (5.7%)	48 (4.4%)	46 (5.2%)
Persistent response[c]	1 (0.7%)	3 (2.0%)	7 (1.1%)	13 (2.1%)	9 (3.0%)	2 (1.9%)	17 (1.6%)	18 (2.0%)
Indeterminate response[d]	2 (1.3%)	2 (1.4%)	13 (2.1%)	9 (1.4%)	7 (2.3%)	2 (1.9%)	22 (1.8%)	13 (1.5%)
Transient response[e]	3 (2.0%)	3 (2.0%)	2 (0.3%)	10 (1.6%)	4 (1.3%)	2 (1.9%)	9 (0.8%)	15 (1.7%)
High Titer	0	2 (1.4%)	1 (0.2%)	3 (0.5%)	0	0	1 (0.1%)	5 (0.6%)
Treatment-boosted response[f]	1 (0.7%)	0	3 (0.5%)	1 (0.2%)	1 (0.3%)	1 (1.0%)	5 (0.5%)	2 (0.2%)
Neutralizing antibodies	3 (2.0%)	5 (3.4%)	10 (1.6%)	14 (2.2%)	2 (0.7%)	1 (1.0%)	15 (1.4%)	20 (2.3%)

a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.
b A positive response in the ADA assay post first dose when baseline results are negative or missing.
c Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.
d Treatment-emergent response with only the last collected sample positive in the ADA assay.
e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.
f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.
g Combined ADA data from placebo 1.14 mL and placebo 2 mL treatments in Study EFC13579
h Includes combined ADA data from placebo 1.14 mL and placebo 2 mL treatments in Study EFC13579
Source: Study EFC14280, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.1.2.2] and [16.2.5.4.1.2.6]

Association of ADA to Adverse Events

Although treatment-emergent ADA positive patients appeared to have lower mean exposure compared with that of ADA negative patients, the individual exposures observed in patients with low to moderate titer ADA response were generally within the exposure range in ADA negative patients (pooled dupilumab 300 mg q2w data in Studies EFC14146 and EFC14280).
Markedly reduced dupilumab exposures were observed in very few patients with high titer ADA responses (N=3 with dupilumab concentration data including one patient who discontinued treatment at Week 20), with dupilumab concentrations that decreased from Week 4 onward and then stayed below or close to LLOQ of the assay (0.078 mg/L). Similarly, in patients who received 300 mg q2w−q4w (Study EFC14280), an association of ADA with PK was only evident in patients with high titer response.
There was no clear evidence of lack or loss of efficacy in patients who developed ADA (including NAb) response with low to moderate titer. Two of the 3 patients who had high titer ADAs and low drug concentration had an apparent lack of treatment effect. It should be noted that ADA was not found to be a significant covariate in the Pop PK analysis (POH0611) or in PK/PD analyses of the primary efficacy endpoints (Study POH0687). The safety profile in patients with a positive ADA status appeared similar to that of patients with a negative ADA status.

Overall, the ADA response in CRSwNP patients is consistent with that observed for asthma and AD patients at the same dupilumab dose and treatment duration (300 mg q2w for 52 weeks) as reported in the original marketing application for AD and the subsequent application for asthma. Analyses of AEs, severe AEs, SAEs, and AEs leading to permanent treatment discontinuation by MedDRA primary SOC and PT were performed for subgroups of patients based on ADA response status. Additionally, focused analyses evaluated the association of hypersensitivity, injection site reaction and serious or severe injection site reactions that lasted 24 hours or more by ADA response status.

Overview of treatment period AEs in the safety pool (studies EFC14146 and EFC14280)

An overview of AEs according to ADA response in the safety pool is provided in Table 50. The limited number of patients with an ADA response made it difficult to draw any conclusion on the potential influence of treatment-emergent ADA response on the incidence of AEs.

There was no apparent imbalance in AE incidence in the few ADA-positive patients (N=26) compared with the ADA-negative patients (N=693). Of the 26 patients who were ADA-positive, 17 patients had AEs, with no apparent pattern or increase in incidence in the few ADA-positive patients compared with the ADA-negative.

A total of 2 ADA-positive patients in the dupilumab group had treatment period AEs that led to permanent treatment discontinuation. In the placebo group, the incidence of permanent treatment discontinuation was higher in ADA negative patients compared to ADA-positive patients (15 [5.5%] versus 0).

In the dupilumab group, 1 ADA-positive patient was diagnosed with **EGPA** on Day 8 after receiving only one dose of IMP that was reported as an SAE. This event was considered serious and resulted in permanent treatment discontinuation. One ADA-positive patient in the dupilumab 300 mg q2w group discontinued treatment due to **lupus-like syndrome.** This was a 53-year-old man with no history of autoimmune disease or lupus who presented with a photosensitive macular rash and digital skin cracks reminiscent of 'mechanics hands' on Day 57 (12 days after the 4th IMP injection). He had no systemic symptoms or signs. The diagnosis was supported by the presence of anti-SSA autoantibodies (anti-Sjogren's–syndrome-related antigen A). He was ADA negative around the time of the event and had an indeterminate low titer ADA response (60) on Day 166. Concomitant medications included mometasone furoate nasal spray, codeine, paracetamol, atorvastatin calcium, levothyroxine sodium, telmisartan, and cophenylcaine. No corrective treatment was given. IMP was permanently discontinued; the last administration was on Day 71 (12 days after the 5th IMP injection). At last visit, the facial rash had also improved significantly; the patient subjectively reported an improvement of 80%. At the time of the last report, the patient had not recovered from the event of lupus-like syndrome but was in stable condition. Both the investigator and the Sponsor assessed the event as possibly related to the IMP.

Table 50 - Overview of AEs according to ADA response: positive, negative - 24 week pooled ADA population

	Placebo		Dupilumab 300mg q2w	
n(%)	ADA positive[a] (N=7)	ADA negative[b] (N=274)	ADA positive[a] (N=19)	ADA negative[b] (N=419)
Patients with any AE	5 (71.4%)	202 (73.7%)	12 (63.2%)	291 (69.5%)
Patients with any severe AE	0	18 (6.6%)	1 (5.3%)	16 (3.8%)
Patients with any SAE	0	16 (5.8%)	1 (5.3%)	14 (3.3%)
Patients with any AE leading to death	0	0	0	0
Patients with any AE leading to permanent treatment discontinuation	0	15 (5.5%)	2 (10.5%)	8 (1.9%)
Patients with any treatment-related AE	1 (14.3%)	45 (16.4%)	3 (15.8%)	84 (20.0%)

[a] Treatment-emergent or treatment-boosted ADA.
[b] Pre-existing immunoreactivity or negative in the ADA assay at all time points.
ADA: Anti-drug antibody, AE: Adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one event
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/pk_ae_overview_pos_neg_s_t.sas OUT=REPORT/OUTPUT/pk_ae_overview_pos_neg_24_s_t_i.rtf (12OCT2018 - 11:22)

The number (%) of patients with at least one AE with incidence ≥5% in either group in the overall population is provided in Table 51. Few events were reported in ADA-positive patients in the dupilumab and placebo treatment groups. The following PTs were reported in dupilumab ADA-positive patients: nasal polyps (3 patients), headache (2 patients), epistaxis and asthma (1 patient for each). For placebo ADA-positive patients 2 patients reported a headache.

Table 51 - Number (%) of patients with AE(s) with PT ≥5% in either group by primary SOC and PT according to ADA response: positive, negative - 24 week pooled ADA population

Primary System Organ Class Preferred Term n(%)	Placebo ADA positive[a] (N=7)	Placebo ADA negative[b] (N=274)	Dupilumab 300mg q2w ADA positive[a] (N=19)	Dupilumab 300mg q2w ADA negative[b] (N=419)
Number of patients with at least one AE with incidence ≥5% in either group	5 (71.4%)	202 (73.7%)	12 (63.2%)	291 (69.5%)
Infections and infestations	2 (28.6%)	118 (43.1%)	5 (26.3%)	135 (32.2%)
Nasopharyngitis	0	41 (15.0%)	0	54 (12.9%)
Nervous system disorders	3 (42.9%)	31 (11.3%)	4 (21.1%)	41 (9.8%)
Headache	2 (28.6%)	22 (8.0%)	2 (10.5%)	30 (7.2%)
Respiratory, thoracic and mediastinal disorders	1 (14.3%)	84 (30.7%)	6 (31.6%)	74 (17.7%)
Epistaxis	0	20 (7.3%)	1 (5.3%)	24 (5.7%)
Nasal polyps	0	33 (12.0%)	3 (15.8%)	9 (2.1%)
Asthma	0	20 (7.3%)	1 (5.3%)	6 (1.4%)
General disorders and administration site conditions	1 (14.3%)	49 (17.9%)	2 (10.5%)	82 (19.6%)
Injection site erythema	0	22 (8.0%)	0	28 (6.7%)

[a] Treatment-emergent or treatment-boosted ADA.
[b] Pre-existing immunoreactivity or negative in the ADA assay at all time points.
ADA: Anti-drug antibody, AE: Adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one event
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group
Only PTs >= 5% in at least one treatment arm overall are presented
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/pk_ae_socpt_5_pos_neg_s_t.sas OUT=REPORT/OUTPUT/pk_ae_socpt_5_pos_neg_24_s_t_i.rtf (12OCT2018 - 12:16)

Hypersensitivity reactions (blinded medical review)

One ADA-positive patient in the dupilumab group experienced a PT of EGPA which was identified within the hypersensitivity narrow SMQ . Upon medical review, this case was considered an auto-immune condition and not a classical immediate or delayed hypersensitivity reaction.

Injection site reactions

Among the 26 ADA-positive patients across both treatment groups, only 1 patient experienced an injection site reaction. Patient No. 014280-036-0003-00210 had injection site pruritus on Days 30 and 45 and had an indeterminate low titer ADA response (60) on Day 166 (95 days after discontinuing treatment due to lupus-like syndrome – described above).

The table below summarizes the frequency of injection site reactions by ADA status for both the placebo and dupilumab treatment groups. The single ADA-positive patient with any injection site reaction had mild injection site pruritus; there were no ADA-positive dupilumab-treated patients with moderate or severe injection site reactions. In the placebo group there were no ADA-positive patients with injection site reactions.

Number (%) of patients with injection site reaction according to ADA response: positive, negative - 24 week pooled ADA population

Category Preferred Term n(%)	Placebo ADA positive[a] (N=7)	Placebo ADA negtive[b] (N=274)	Dupilumab 300mg q2w ADA positive[a] (N=19)	Dupilumab 300mg q2w ADA negtive[b] (N=419)
Number of patients with at least one injection site reaction	0	34 (12.4%)	1 (5.3%)	60 (14.3%)
Number of patients with at least one ISR (Mild)	0	31 (11.3%)	1 (5.3%)	57 (13.6%)
Number of patients with at least one ISR (Moderate)	0	3 (1.1%)	0	2 (0.5%)
Number of patients with at least one ISR (Severe)	0	0	0	1 (0.2%)
Number of patients with at least one ISR (Serious)	0	0	0	0

[a] Treatment-emergent or treatment-boosted ADA.
[b] Pre-existing immunoreactivity or negative in the ADA assay at all time points.
ADA: Anti-drug antibody, PT: Preferred term
MEDDRA 21.0
n (%) = number and percentage of patients with at least one event
Note: Table sorted by decreasing percentage of PT in dupilumab 300 mg q2w group
Source: 2.7.4 [Table 53]

Serious or severe (lasting more than 24 hours) injection site reactions

Only 1 patient (014280-620-0001-00209, dupilumab group) had a serious or severe injection site reaction that lasted more than 24 hours. This patient was ADA negative.

Safety in special populations

Intrinsic factors (safety pool)

Adverse events
Dupilumab treatment was not associated with an increase in the proportion of patients with treatment period AEs compared with placebo treatment for demographic subgroup categories. The number of patients in the category Black/of African descent were too few to draw any meaningful conclusions. Dupilumab treatment was not associated with an increase in the proportion of patients with treatment period AEs compared with placebo regardless of baseline level of eosinophils.

SAEs, AEs leading to permanent treatment discontinuation, and AEs of special interest and other selected AE groupings
Overall, a small number of patients experienced treatment-period SAEs, AEs leading to permanent treatment discontinuation, or AESIs or AEs in other selected groupings. Meaningful analyses of these AEs by subgroups defined by intrinsic factors (ie, baseline demographics, baseline blood eosinophil count, and baseline disease characteristics) were not possible.

Overview of adverse event profile by age groups
Because there was only one patient in the ≥85 years category, that age category is not provided in Table 57. The 85-year-old patient was in the placebo group; he experienced TEAEs of nasopharyngitis, 3 events of hypertensive crisis (verbatim term: worsening of pre-existing hypertension) and 1 event of hypertension (verbatim term: unstable arterial hypertension). The patient recovered from these events. As shown in Table 57, overall incidence of AEs, SAEs, and discontinuations due to AEs increased with age. In both subgroups of patients <65 years old and ≥65 years old, the incidence of AEs, SAEs, and discontinuations due to AEs was lower in the dupilumab group compared to the placebo group.

Table 57 - Overview of adverse event profile by age groups - 24 week pooled safety population

Category System Organ Class	Age < 65 years		Age 65-74 years		Age 75-84 years	
	Pbo (N=237) n (%)	Dup (n=361) n (%)	Pbo (N=37) n (%)	Dup (n=68) n (%)	Pbo (N=7) n (%)	Dup (n=11) n (%)
Patients with any AE	175 (73.8%)	247 (68.4%)	26 (70.3%)	50 (73.5%)	6 (85.7%)	8 (72.7%)
Patients with any SAE	11 (4.4%)	11 (3.0%)	3 (8.1%)	3 (4.4%)	2 (28.6%)	1 (9.1%)
Patients with any AE leading to treatment discontinuation	12 (5.1%)	9 (2.5%)	2 (5.4%)	2 (2.9%)	1 (14.3%)	0
Infections and infestations	101 (42.6%)	122 (33.8%)	15 (40.5%)	16 (23.5%)	3 (42.9%)	3 (27.3%)
Respiratory, thoracic and mediastinal disorders	71 (30.0%)	67 (18.6%)	9 (24.3%)	12 (17.6%)	5 (71.4%)	1 (9.1%)
General disorders and administration site conditions	40 (16.9%)	74 (20.5%)	9 (24.3%)	10 (14.7%)	1 (14.3%)	0
Gastrointestinal disorders	32 (13.5%)	48 (13.3%)	4 (10.8%)	10 (14.7%)	1 (14.3%)	1 (9.1%)
Nervous system disorders	31 (13.1%)	41 (11.4%)	1 (2.7%)	3 (4.4%)	2 (28.6%)	1 (9.1%)
Musculoskeletal and connective tissue disorders	22 (9.3%)	45 (12.5%)	2 (5.4%)	5 (7.4%)	2 (28.6%)	3 (27.3%)
Injury, poisoning and procedural complications	22 (9.3%)	26 (7.2%)	3 (8.1%)	9 (13.2%)	2 (28.6%)	1 (9.1%)
Skin and subcutaneous tissue disorders	13 (5.5%)	24 (6.6%)	5 (13.5%)	2 (2.9%)	0	0
Vascular disorders	10 (4.2%)	9 (2.5%)	3 (8.1%)	5 (7.4%)	1 (14.3%)	0

AE: Adverse event, SOC: System organ class, SAE: Serious adverse event
MEDDRA 21.0
n (%) = number and percentage of patients with at least one AE
Treatment period is from first administration of IMP to the earliest of study day 169 (Week 24) or last administration of IMP + 98 days.
PGM=PRODOPS/SAR231893/OVERALL/ISS_NP_2018/REPORT/PGM/sub_soc_s_t.sas OUT=REPORT/OUTPUT/sub_soc_by24_s_t_x.rtf (29NOV2018 - 3:01)

Extrinsic factors (safety pool)

The incidence of any treatment period AE, SAE, AE leading to permanent treatment discontinuation, and any AESI/other selected AE grouping (SMQ/CMQ) by category was assessed for extrinsic factors using the same methodology as described for intrinsic factors.
Extrinsic factors were:
• Region (Asia, Latin America, Eastern Europe, Western Countries)
• Territory (North America, European Union, Rest of World)

Adverse events
Dupilumab treatment was not associated with an increase in the proportion of patients with treatment period AEs compared with placebo treatment for extrinsic subgroup of region and territories.

SAEs, AEs leading to permanent treatment discontinuation, and AEs of special interest and other selected AE groupings
The same applies for extrinsic factors of Region and Territory (ie, meaningful comparisons were not possible due to the small number of patients who experienced SAEs, AEs leading to permanent treatment discontinuation, and AEs of special interest and other selected AE groupings).

Use in pregnancy and lactation

No pregnancies or partner pregnancies were reported in Study ACT12340. Due to the small number of pregnancies in patients exposed to dupilumab in the clinical studies, the current data are insufficient to inform the pregnancy risks associated with dupilumab exposure. Available data to date provide no evidence that dupilumab has an adverse effect on pregnancy or pregnancy outcomes.
In order to acquire more data on any effects on pregnancy associated with dupilumab exposure, a pregnancy registry has been established to compare the pregnancy outcome, between patients with and patients without dupilumab treatment.

Overdose

No cases of symptomatic overdose with IMP were reported in the pooled safety population or in supportive Study ACT12340.

Drug abuse

Based on the reported TEAEs in the dupilumab clinical studies (AD, asthma, and CRSwNP indications) and postmarketing data, there is no suggestion that dupilumab affects central nervous system activity or is associated with signs of drug abuse.

Withdrawal and rebound

In Study EFC14146, post-treatment AE incidence was similar in the dupilumab 300 mg q2w group and placebo groups. The most frequently reported post-treatment AEs were nasal polyps and nasopharyngitis in the dupilumab and placebo groups. Overall AE rates were lower than observed during the 24 week treatment period in both groups.
In Study EFC14280, which has ongoing follow-up, post-treatment AE incidence was higher in the placebo group than in the dupilumab 300 mg q2w and the dupilumab 300 mg q2w-q4w groups. Overall AE rates were lower than observed during the treatment period. There does not appear to be an increased incidence of AEs after withdrawal of dupilumab treatment.

Treatment-emergent adverse events comparison in the atopic dermatitis, asthma, and CRSwNP studies - safety pools

	Atopic Dermatitis Studies[a]			Asthma Studies[b]			CRSwNP Studies[c]	
		Dupilumab			Dupilumab			Dupilumab
No. of patients with at least 1 TEAE	Placebo (N=517) n (%)	300 mg q2w (N=529) n (%)	300 mg qw (N=518) n (%)	Placebo (N=792) n (%)	200 mg q2w (N=779) n (%)	300 mg q2w (N=788) n (%)	Placebo (N=282) n (%)	300 mg q2w (N=440) n (%)
CMQ: Conjunctivitis – narrow	11 (2.1%)	49 (9.3%)	41 (7.9%)	17 (2.1%)	10 (1.3%)	14 (1.8%)	1 (0.4%)	7 (1.6%)
CMQ: Conjunctivitis - broad	14 (2.7%)	60 (11.3%)	57 (11.0%)	24 (3.0%)	12 (1.5%)	21 (2.7%)	1 (0.4%)	12 (2.7%)
HLT: Herpes viral infections	18 (3.5%)	34 (6.4%)	25 (4.8)	16 (2.0%)	9 (1.2%)	10 (1.3%)	2 (0.7%)	7 (1.6%)
HLT: Eosinophilic disorders	2 (0.4%)	9 (1.7%)	1 (0.2%)	2 (0.3%)	21 (2.7%)	18 (2.3%)	1 (0.4%)	5 (1.1%)
PT: Eosinophil count increased	0	2 (0.4%)	3 (0.6%)	2 (0.3%)	8 (1.0%)	7 (0.9%)	0	1 (0.2%)
SOC: Hepatobiliary disorders	2 (0.4%)	2 (0.4%)	1 (0.2%)	4 (0.5%)	12 (1.5%)	18 (2.3%)	0	0
SOC: Hepatobiliary disorders (serious adverse events)	0	0	0	1 (0.1%)	2 (0.3%)	5 (0.6%)	0	0
SOC: Cardiac disorders	4 (0.8%)	3 (0.6%)	5 (1.0%)	11 (1.4%)	11 (1.4%)	19 (2.4%)	6 (2.1%)	2 (0.5%)
SOC: Cardiac disorders (serious adverse events)	1 (0.2%)	1 (0.2%)	2 (0.4%)	0	4 (0.5%)	10 (1.3%)	1 (0.4%)	1 (0.2%)
PT Hypertension	8 (1.5%)	9 (1.7%)	6 (1.2%)	12 (1.5%)	18 (2.3%)	10 (1.3%)	3 (1.1%)	12 (2.7%)
PT Arthralgia	10 (1.9%)	16 (3.0%)	5 (1.0%)	30 (3.8%)	18 (2.3%)	22 (2.8%)	5 (1.8%)	14 (3.2%)

In only one asthma study (EFC13579), a numerical imbalance between dupilumab and placebo was observed for SAEs under (MedDRA SOC) cardiac disorders (0 of 634 in placebo, 4 of 631 [0.6%] in the 200 mg q2w and 10 of 632 [1.6%] patients in 300 mg q2w dupilumab group).
However, a broad database search for CV events followed by a blinded adjudication analysis by 3 independent cardiologists did not support a notable difference in the safety profile between dupilumab and placebo for MACE, MACE plus hospitalization for unstable angina events, as well as for CV deaths. A similar imbalance has not been observed in any other placebo controlled study in asthma, AD, or CRSwNP.
Additionally, in rare cases patients in asthma studies have reported eosinophilic conditions such as EGPA and eosinophilic pneumonia, which are a known disease risk in asthma and in CRSwNP but not in AD. In accordance with the disease background, they were not observed in the dupilumab AD clinical trials.
In asthma Study EFC13579, a numerically greater proportion of patients reported TEAEs under (MedDRA SOC) hepatobiliary disorders in the dupilumab group than placebo. A similar imbalance has not been observed in any other placebo controlled study, either in asthma, AD and CRSwNP.

In addition, PTs of hypertension and arthralgia, which had higher relative risk in dupilumab treated patients in the CRSwNP studies, were compared to the AD and asthma indications. The rates for these PTs were similar to those observed in patients with AD and asthma treated with dupilumab 300 mg q2w.

Post marketing experience

No new significant safety concerns have been identified from the post-marketing data in the recently submitted PSUR which covered the period of 27 March 2018 to 28 September 2018.

2.5.1. Discussion on clinical safety

A total of 722 patients were included in the conducted phase 2 and 3 studies (ACT12340, EFC14146, and EFC14280), of which 470 CRSwNP patients were exposed to dupilumab in the claimed indication. Thus, the safety database for the CRSwNP clinical program includes a total of 470 patients exposed to dupilumab: 30 patients who received 300 mg qw (ACT12340), and 440 patients who received dupilumab 300 mg q2w (EFC14146, and EFC14280). Of the patients who received 300 mg q2w, 292 patients exclusively received 300 mg q2w (EFC14146 and EFC14280) and 148 patients received 300 mg q2w for 24 weeks followed by 300 mg q4w (EFC14280). The safety database was considered adequate by the CHMP.

The pooled safety data comprises data from adult patients with CRSwNP who received dupilumab 300 mg q2w for 24 weeks without data from the phase 2 proof-of-concept study ACT12340 due to a limited number of patients, a shorter treatment period and a different dosing regimen. The pooling strategy was endorsed by the CHMP.

During all studies Dupixent was administered subcutaneously, the dosing regimen differed between the phase 2 study and the two pivotal phase 3 studies; therefore, the data of the phase 2 study is regarded as supportive safety data since it has not been included in the safety pool. Both phase 3 studies used the approved dose regimen for the atopic dermatitis and asthma indications as per product information (300 mg q2 SC) during the first 24 weeks on a background therapy of mometasone furoate nasal spray (MFNS). Only patients enrolled in study EFC14280 continued the dupilumab treatment up to week 52, partially receiving a modified dose regimen (300 mg q4w SC). The primary and co-primary endpoints were consistently assessed during all three studies. The majority (96.6%) of the patients randomized in studies EFC14146 and EFC14280 that received the verum completed the treatment within the planned treatment period of 24 weeks (96.1%) and received 11 or more dupilumab injections (96.6%) and merely a small part of these patients (3.4%) discontinued the treatment prior to week 24 mainly due to adverse events (2%). The overall exposure was higher in the dupilumab group (198.06 PY) compared with the placebo group (124.76 PY) due to the additional dupilumab treatment arm in Study EFC14280. The higher exposure of male patients can be explained by the epidemiology (predominance of male sex and asthma observed in CRSwNP and CRSsNP). The IMP compliance was high and similar in both treatment groups (placebo 99.3% vs. verum 99.8%) as well as the MFNS compliance (both 92%). The demographic and disease line characteristics were fairly balanced between the treatment groups (placebo/verum). All enrolled patients suffered from severe CRSwNP, as evidenced by significant nasal polyp size, significant symptoms, poor baseline sense of smell, extensive sinus disease, and poor QOL with a mean time since the first diagnosis of CRSwNP of nearly 11 years and almost two thirds of the patients had already undergone surgery at least once. Seventy four point five (74.5%) of all patients were treated with systemic corticosteroids, 60% had a history asthma and the majority of patients (79.8%) had a comorbid type 2 inflammatory disease. The number of patients treated for 6 months at dosage levels intended for clinical use is considered large enough according to ICH E1. Hence, the patient exposure in the CRSwNP safety database is considered acceptable.

Sixty nine (69%) of the dupilumab group and 74% of the placebo group had AEs during the treatment period. The infections and infestations SOC had the highest proportion of patients showing AEs with a lower percentage in the verum group vs. the placebo group (32% vs. 42.6%) with nasopharyngitis as predominant symptom. The most frequently reported PTs in the dupilumab and placebo groups were epistaxis, cough, nasal polyps and asthma, overall with a lower incidence in the dupilumab group. The general disorders and administration site conditions SOC had the third highest proportion of patients with AEs (mainly due to injection site reactions).

Dupilumab treatment was associated with a higher incidence of ISR (3.4% versus 1.8%), as already observed during the AD and asthma studies and during the administration of other subcutaneously administered monoclonal antibodies, arthralgia (3.2% versus 1.8%), hypertension (2.7% versus 1.1%), insomnia (1.4% versus 0%), conjunctivitis (1.4% versus 0%) and injection site swelling (1.4% versus 0.4%). Most ISR were mild to moderate and only one severe AE case occurred and neither SAEs nor treatment discontinuations were recorded.

Among CRSwNP patients the frequency of conjunctivitis was higher in dupilumab than placebo. Conjunctivitis is already listed in the SmPC for the AD population. This is investigated in the ongoing ophthalmology study described in the RMP.

The arthralgia incidence is relatively similar to that observed during the asthma population with regard to the same dose (2.8%). Again, most cases were mild to moderate, one severe case was associated with other symptoms during steroid tapering and no significant association to ADA formation was detected.

Two deaths occurred outside the 24-week-treatment period: One death occurred in the placebo group (suspected myocardial infarction in the post-treatment period of Study EFC14146) and one in the verum group (traumatic intracranial hemorrhage 72 days after the last (26th) IMP injection);

both were considered unrelated to the IMP which seems plausible according to the provided information. Hence, no further inquiries of these two cases are prompted.

The severe TEAE rates were low in general for both the safety pool and the placebo group. A lower proportion of patients in the dupilumab treatment group experienced other serious adverse events (3.4% vs. 5.7 % placebo group) and no distinct SAE pattern became obvious. The minimally higher incidence of nasal polyps and asthma in the placebo group reflects a probable protective effect of dupilumab.

Dupilumab-related SAEs relate to one case with eosinophilia and EGPA which led to treatment discontinuation due to their intensity. Individual cases of EGPA and eosinophilic pneumonia were reported and recorded during asthma study LTS12551 and these patients had a clinical history suggestive of pre-existing systemic eosinophilic conditions or underwent steroid tapering. In general, eosinophilia TEAEs occurred at a higher frequency in the dupilumab groups compared with the placebo groups during the dupilumab development program and this phenomenon is explainable by the mechanism of action (see also discussion below on AESIs).

The number of subjects experiencing TEAEs leading to study drug discontinuation was low in general in the dupilumab treatment and placebo groups (2.5% vs. 5.3%). Within the verum group discontinuation rates reached a plateau after week 15 and decreased during the following weeks. No special TEAE pattern which could have led to study drug discontinuation is discernible.

AESI were numerically fairly balanced between the treatment groups: Injection site reactions/swelling (predefined AESI: serious or severe injection site reactions lasting 24 hours or longer (0.2% vs. 0% in dupilumab treated group and placebo respectively)), conjunctivitis (broad, 2.7% vs. 0.4 %) and eosinophilia (1.4% vs. 0.4%) occurred more often in the dupilumab treatment group whereas epistaxis (7.1% vs. 5.7%) and infections (1.8% vs. 0.9%) were more common in the placebo group.

Injection site reactions (ISR) clearly constitute the largest category of AESI, the incidence remained relatively stable over time and decreased after week 15, under dupilumab administration. Hypersensitivity reactions which include severe ISR (lasting longer than 24 hrs) are considered to be an important potential risk and belong to the predefined AESI on the basis of the hitherto known safety profile. In the AD population severe ISR were rare (1.4% in the 300 mg Q2W group) in general and 0.6-1.6% discontinued the IMP due to an ISR. During the AD program only one patient included in the OLE study (R668-AD-1225 OLE study) was presented to have experienced a severe ISR. With regards to the similar dose and treatment duration (300 mg Q2W, 52-week data) 14.5% showed ISR in general, which is a similar percentage compared with the CRSwNP population.

No patient in the safety pool had an anaphylactic reaction and the proportion of patients who experienced potential systemic hypersensitivity was low and balanced between treatment groups. Individual cases led to treatment discontinuation (macular rash and drug hypersensitivity with rash and diarrhea).

One severe treatment-related injection site reaction was experienced by a dupilumab-treated patient. Three dupilumab-treated patients had 3 SAEs of infection, one of them recovered with sequelae; these cases were considered unrelated to dupilumab by the investigator. No other infections were recorded.

Moreover, no cases of malignancies or suicidal behaviour were registered.

Conjunctivitis had a higher percentage in the dupilumab group (1.6%) compared with the placebo group (0.4%) but ranges around the percentage registered during the asthma development program (2.7% in the 300 mg Q2W group) and is generally lower than in the AD population (8%) although this very study population had relevant comorbidities like asthma etc.

Special attention was focused on eosinophilia since this phenomenon is known to be associated with dupilumab treatment and was already discussed during the MAA for AD and asthma, it is therefore reflected as common ADR in the RMP and SmPC. Treatment-emergent eosinophilia was generally observed to be of transient nature and is attributed to the dupilumab-induced inhibition of eotaxin that consequently hampers the ingress of eosinophils into target tissues. The eosinophilia frequency observed in the safety pool was consistent to that one observed in the AD

and asthma program (1%). Across both pivotal studies through the treatment-emergent period, a total of 12 patients experienced TEAEs in the eosinophilia CMQ, thereof were 4 SAEs and associated with clinical symptoms in dupilumab-treated patients (3 EGPA and 1 eosinophilia, thereof two considered possibly related and two unrelated), they were also severe, and led to permanent treatment discontinuation. 4 mild or moderate eosinophilia TEAEs without any associated clinical sign were recorded in the dupilumab group. Therefore, an update of the warning section 4.4 is introduced as follows *: Cases of vasculitis consistent with EGPA have been reported with dupilumab and placebo in adult patients with co-morbid asthma in the CRSwNP development program".*

Three cases of cardiovascular events (CV) gathered in the cardiac disorders SOC, nervous system disorders SOC, vascular disorders SOC, with a PT of pulmonary embolism occurred in dupilumab-treated patients; thereof one case of MI was finally assessed as CV event and considered unrelated to dupilumab. Hence, no significant cardiac impact of dupilumab was observed.

No new ADRs were identified in the CRSwNP program. Amongst ADRs observed in dupilumab-treated patients in the AD and/or asthma programs, injection site reaction, injection site swelling and conjunctivitis are considered ADRs in the CRSwNP program as these events demonstrated an imbalance in the dupilumab group(s) compared to the placebo group, though the rate of these ADRs was lower as compared with the other dupilumab clinical programs. The ADR analysis, interpretation and classification endorsed and already covered in section 4.8 of the SmPC.

No significant difference of patients with abnormalities of RBC and platelet count (PSCA) was observed between the verum and the placebo group and percentages reflecting changes of these laboratory parameters were generally lower in the dupilumab treatment group apart from Hb changes ≤ 115 g/L (Male); ≤ 95 g/L (Female) (1.9% vs. 1.1%). No relevant mean changes from baseline were observed for WBC parameters in both treatment groups in the safety pool except the relatively often detected increase of eosinophils with a higher incidence in the dupilumab group (25.3% vs. 13.7%) resulting in 4 SAEs of eosinophilia and EGPA in 4 different patients. Treatment-emergent eosinophilia constitutes a known and already extensively discussed TEAE/AESI (see above). The post-baseline eosinophil counts increased in patients receiving dupilumab with baseline blood eosinophil counts <0.5 Giga/L rising to ≥0.5 Giga/L and <1 Giga/L (DUP 27.0% vs. PLAC 22.3%), a greater increase to ≥1 Giga/L and <1.5 Giga/L was seen in DUP 7.2% vs. PLAC 1.6% suggesting a moderate and transient effect of dupilumab on eosinophil counts. No adverse effects on clinical chemistry parameters (metabolic parameters, electrolytes, renal and liver function parameters) were recorded.

No relevant changes as to vital signs or physical examinations were registered.

Overall, approximately 4% of study subjects in the 24 weeks safety pool receiving dupilumab 300 mg q2w and 2% of those in the placebo groups developed ADA as treatment-emergent response.

Patients treated with dupilumab during the 52-week study EFC14280 showed a treatment-emergent ADA response in 5% and 8%, respectively, depending on the dose regimen (300 mg q2w or 300 mg q2w-q4w). In comparison, patients enrolled in 24 week study EFC14146 (300 mg q2w) developed treatment-emergent ADA response in 15% of all cases vs. 5% noted in the placebo group. However, in the follow-up period for each study, ADA positive responses in dupilumab patients (total 40 of 415 patients across both studies) did not correlate with safety findings, with no temporal relationship between ADA formation and the occurrence of SAEs or AESIs.

Within the safety pool, persistent ADA response was observed in 1.6% of all patients at 300 mg q2w compared to 0.7% for placebo. Most cases had low ADA titers and high titer ADA response was observed in 0.9-1.4% (24 weeks safety pool and 52-week study EFC14280, 300 mg q2w) of the patients. As seen in the asthma population, an inverse relationship between ADA incidence and cumulative monthly dose was observed (study EFC14280), thus, lower ADA incidence was associated with a higher dose frequency. Neutralising antibodies ranged between 2-3% (24 weeks safety pool and 52-week study EFC14280, 300 mg q2w) and 15% (EFC14146). The overall ADA incidence seen in the safety pool is slightly lower than in the asthma program (6%) and the AD program (<10% with persistent treatment-emergent ADA-positive response <2% in the primary safety pool).

Two ADA-positive patients in the dupilumab group had treatment period AEs that led to permanent treatment discontinuation and one ADA-positive patient developed an EGPA after one dupilumab administration which consecutively was stopped.

Some events were reported in ADA-positive patients in the dupilumab and placebo treatment groups and no distinct pattern was discernible in ADA-positive study subjects (nasal polyps (3 patients), headache (2 patients), epistaxis and asthma (1 patient for each).

No increased risk was apparent for TEAEs with dupilumab treatment compared with placebo in any of the intrinsic factor subgroups examined (ie, age, sex, race, ethnicity, weight, BMI, baseline blood eosinophil count, prior nasal polyp surgery (yes/no), asthma (yes/no) asthma and/or NSAID-ERD, and NSAID-ERD (yes/no). The same applies to extrinsic factors. There does not appear to be an increased incidence of AEs after withdrawal of dupilumab treatment.

Supportive data:

During study ACT12340 all 30 included patients receiving dupilumab experienced at least one TEAE, thereof were 6.7% SAE, 6.7% had TEAE that led to treatment discontinuation; no death occurred.

The most frequently reported TEAE in the dupilumab group vs. the placebo group were nasopharyngitis (46.7% vs. 33.3%), injection site reaction (40.0% vs. 6.7%), epistaxis (23.3% vs. 6.7%), oropharyngeal pain (23.3% vs. 6.7%), headache (16.7% vs. 20.0%). One injection site reaction recorded in the verum group led to a treatment discontinuation. Overall, injection site erythema was the most frequently reported symptom, followed by injection site pain. Imbalances for epistaxis and oropharyngeal pain were also observed in this study, 7 patients (23.3%) in the dupilumab group compared with 2 (6.7%) patients in the placebo group for both PTs.

Two patients treated with dupilumab experienced SAEs (one AESI with herpes zoster and the other with arrhythmia, pain in extremity, hypoaesthesia, and mononeuropathy); they were considered unrelated to the study drug.

Overall, 2 treatment discontinuations were recorded in the dupilumab group, one due to a moderateISR and one due to constipation.

No TEAEs of eosinophilia or blood eosinophil count increases were reported.

Four patients exposed to dupilumab were ADA positive during the study, all four had injection site reactions. In general, the 16-week treatment seems to reveal the same safety profile observed during the two pivotal studies EFC14146 and EFC14280. The higher incidence of ISR is explainable by the higher treatment frequency.

Based on the hitherto presented and available data, dupilumab treatment seems to have an acceptable safety profile, since it did not lead to opportunistic infections, skin disorders, neoplasms, musculoskeletal and connective tissue disorders, gastrointestinal disorders or cardiovascular disorders. With regard to TEAE profile, no meaningful qualitative and quantitative differences were seen as to short-term and long-term treatment apart from injection site reactions. No new identified risks became apparent in the CRSWNP population.

2.5.2. Conclusions on clinical safety

In the safety pool, there were 6 AEs reported at ≥1% incidence and with a 1% higher incidence in the dupilumab group than in placebo group were: hypertension, arthralgia, insomnia, injection site reaction, injection site swelling, and conjunctivitis.

While injection site reactions, injection site swelling and conjunctivitis are known, arthralgia, insomnia and hypertension are not, further information was requested to be provided. The updated information provided by the MAH did not lead to the need for updated information in section 4.8.

Overall, dupilumab treatment appears to be well tolerated, including the proposed dose regimen and method of administration (300 mg Q2Q SC). The safety profile observed during the CRSwNP studies is consistent with the important identified risks mentioned in the safety specification and confirmed the safety profile established during the AD and asthma development programs. The safety profile in this indication is considered acceptable by the CHMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC Rapporteur assessment report. The main changes include consolidation with other RMPs versions, removal of missing information in paediatrics to align with GVP V, removal of malignancy as important potential risk and amendment of safety concerns to specify subpopulations. Studies which have been completed and PIP studies are removed from the RMP in line with EMA guidance. Accordingly, the applicant provided an updated risk management plan version 4.1.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 11 Summary of the safety concerns

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women Conjunctivitis related events in AD patients Long-term safety

Pharmacovigilance plan

Table 12 Ongoing and planned required additional pharmacovigilance activities (by the competent authority) (category 3)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes in asthma and AD patients.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018) Will also be submitted to other health authorities.
			Amended protocol (asthma cohorts)	Will be submitted once available
			Final report	Will be submitted once available
Pregnancy Outcomes Database Study (R668-AD-1760) Planned	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.	Use in pregnant and lactating women	Protocol submission	Will be submitted once available
			Final report	Will be submitted once available
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041) Ongoing	To assess the long term safety, efficacy, PK, and immunogenicity of REGN668 in adult patients with moderate-to-severe AD.	Long term safety (Ophthalmology sub study: additional information on conjunctivitis related events in AD patients)	Final report	Q3 2023
An open-label extension study to assess the long-term safety of	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long term safety of dupilumab in pediatric patients with AD	Final report	4Q 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing				

AD: Atopic Dermatitis; PK: Pharmacokinetics; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

Risk minimisation measures

Table 13 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Important potential risk		
None		
Missing information		
Use in pregnant and lactating women	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639) in asthma and AD patients Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Conjunctivitis related events in AD patients	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ophthalmology substudy in R668-AD-1225

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term safety	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

Dupixent 300 mg solution for injection in pre-filled syringe

As a consequence of this new indication on patients with CRSwNP, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include pharmacological, efficacy and safety data. The Package Leaflet (PL) is updated accordingly.

Additionally minor editorial QRD changes on excipients to the SmPC are introduced in section 6.6 in the 300mg and 200mg strength accordingly. Corresponding changes are implemented in the 200mg strength. Consequently the Annex IIIA is updated.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

The MAH will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use in a separate variation. This was requested by CHMP following procedure EMEA/H/C/004390/X004G.The user testing was submitted in variation EMEA/H/C/004390/II/0018 assessed in parallel of this application.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dupixent (Dupilumab) is included in the additional monitoring list as).

it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

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3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic rhinosinusitis (CRS) is a heterogeneous disease characterized by inflammation of the nose and paranasal sinuses, tissue oedema, nasal obstruction, and increased mucus production causing symptoms including nasal congestion/obstruction (NC), loss of sense of smell, and rhinorrhea that persist for at least 12 week.

Current medical consensus divides CRS into two major phenotypes based on the presence or absence of nasal polyps: chronic rhinosinusitis with nasal polyposis (CRSwNP) and chronic rhinosinusitis without nasal polyposis (CRSsNP). The clinical dichotomization of CRSwNP versus CRSsNP is also reflected at the molecular level, with a heterogeneity of inflammation in patients with CRSsNP and a predominance of type 2 inflammation in patients with CRSwNP. The diagnosis of CRS is established by the presence of at least two rhinosinusitis symptoms and the opacification of sinuses in the computerized tomography (CT) scan. The presence of nasal polyps via the nasal endoscopic examination determines the final diagnosis of CRSwNP. In CRSwNP, nasal polyps are edematous inflammatory lesions, usually bilateral, originating from the mucosa of the ethmoid sinus, maxillary and sphenoidal regions that protrude into the nasal cavities and obstruct the upper airways. CRSwNP affects up to 4% of the adult population and commonly overlaps with other type 2 inflammatory disease, such as asthma. CRSwNP, particularly more severe variants, is associated with significant morbidity and decreased quality of life (QoL) making this disease clinically important to identify, evaluate, and treat. Asthma is a very common type-2 inflammatory comorbid disease in patients with severe CRSwNP (40% to 67%) and these patients have more severe CRSwNP disease characterized by high nasal polyp recurrence rates, corticosteroid dependence, and poor asthma control.

3.1.2. Available therapies and unmet medical need

Available treatments for CRSwNP are limited to the chronic use of intranasal corticosteroids, short courses of systemic steroids when symptoms worsen and surgery when medical therapy fails. These treatment options have major limitations as they treat only one facet of the disease (ie, the local presentation in the nasal cavity), but fail to address the underlying sinus inflammatory disease, a critical facet from which nasal polyposis (NP) originates. The only available systemic treatment, systemic corticosteroid (SCS) can only be used intermittently due to well-known adverse effects with chronic use. Consequently, the underlying inflammation causing this disease is not adequately suppressed by existing therapies resulting in inadequate treatment efficacy, high recurrence rates of nasal polyps post-surgery and overall poor health-related quality of life (HRQoL). Therefore, there is a need for a therapeutic approach.

3.1.3. Main clinical studies

The applicant performed two pivotal studies in support this variation application.

Study EFC14146 was a randomized, double-blind, placebo-controlled, parallel group phase III study. The study consisted of 3 periods a run-in period of 4 weeks, a treatment period of 24 weeks and a post treatment period of 24 weeks. In this study a total of 276 patients with CRSwNP were randomized 1:1 to Dupilumab 300 mg q2w or Placebo. Two co-primary endpoints, change from baseline to week 24 in NPS and change from baseline to week 24 in NC, were planned with the protocol. Furthermore, six key secondary endpoints were planned to be tested in hierarchical order

in order to account for multiplicity: 1) change from baseline in TSS at week 24, 2) change from baseline in UPSIT at week 24, 3) change from baseline in loss of smell daily symptoms at week 24, 4) change from baseline in SNOT-22 at week 24, 5) change from baseline in LMK score at week 24, and 6) proportion of patients with SCS rescue or surgery for NP during the treatment period.

Study EFC14280 was a randomized, double-blind, placebo-controlled, parallel arm phase III study. The study consisted of a run-in period of 4 weeks, a randomized treatment period of 52 weeks, where patients in Arm B were switched to dupilumab q4w dosing regimen at week 24 and a posttreatment period of 12 weeks. In total 448 subjects were randomized 1:1:1 to Dupilumab 300 mg q2w (arm A), Dupilumab 300 mg q2w/q4w (arm B) or Placebo (arm C). Two co-primary endpoints, change from baseline to week 24 in NPS and change from baseline to week 24 in NC, were planned with the protocol (pooled arms A+B vs. C). Furthermore, six key secondary endpoints were planned to be tested in hierarchical order in order to account for multiplicity: 1) change from baseline in TSS at week 24 (pooled arms A+B vs. C), 2) change from baseline in UPSIT at week 24 (pooled arms A+B vs. C), 3) change from baseline in loss of smell daily symptoms at week 24 (pooled arms A+B vs. C), 4) change from baseline in SNOT-22 at week 24 (pooled arms A+B vs. C), 5) change from baseline in LMK score at week 24 (pooled arms A+B vs. C), 6) proportion of patients with SCS rescue or surgery for NP during the treatment period, 7) change from baseline in NPS at week 52 (A vs. C), 8) change from baseline in NC at week 52 (A vs. C), 9) change from baseline in NPS at week 52 (B vs. C), and 10) change from baseline in NC at week 52 (B vs. C).

The patient population in the pivotal studies consisted of patients 18 years and older with high CRSwNP disease burden (based on polyps score) and symptoms of NC and loss of smell or rhinorrhea for at least 12 weeks prior to randomization (8 weeks prior to screening) despite therapy with intranasal corticosteroids, systemic corticosteroids in the past 2 years or sino-nasal surgery.

In addition, study ACT12340 was submitted as a supportive study. It was a proof of concept Phase 2 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the effect of 600 mg loading dose followed by 300 mg given every week.

The dose regimens for the pivotal studies were selected based on the totality of clinical evidence in the dupilumab program including data from Phase 2 efficacy and safety study (ACT12340) in patients with nasal polyps and symptoms of chronic sinusitis. The dose regimen of an initial dose of 300 mg followed by 300 mg given every other week is considered the appropriate posology in patients.

3.2. Favourable effects

Both pivotal studies (EFC 14146 and EFC 14280) showed a significant improvement in patients receiving treatment with dupilumab as compared to those on placebo. The significant difference between the treatment group and the placebo group was observed for the primary endpoints bilateral endoscopic nasal polyposis score (NPS) and nasal congestion/obstruction (NC) symptom score compared with placebo at week 24 and all secondary endpoints including LMK, TSS, UPSIT, SNOT-22.

In both pivotal studies statistical significance was reached for the 2 co-primary efficacy endpoints and all multiplicity adjusted key secondary endpoints demonstrating that dupilumab treatment on top of intranasal corticosteroid improved endoscopic, radiologic and clinical measures of CRSwNP compared to intranasal corticosteroid alone. The hierarchical testing procedure remained intact through all endpoints tested.

In relation to nasal polyposis score (NPS) at week 24, in both pivotal studies statistically significant improvement was observed in the dupilumab group (arm A in study EFC14146 and pooled arm A + B in study EFC14280) with slightly better results reported in study EFC14146.

In study EFC 14146 the LS mean change in NPS from baseline to Week 24 was -1.89 for 300 mg q2w dupilumab and +0.17 for placebo. The LS mean difference versus placebo: -2.06 with 95% CI: -2.43 to -1.69 (p<0.0001). The LS mean change in NC from baseline to Week 24 was -1.34 for the dupilumab group and -0.45 for the placebo group (LS mean difference versus placebo: -0.89 with 95% CI: -1.07 to -0.71; p<0.0001).

In study EFC 14280 the LS mean change in NPS from baseline to Week 24 was -1.71 for the 300 mg q2w dupilumab group (pooled Arm A+B) and was +0.10 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -1.80 with 95% CI: -2.10 to -1.51 (p <0.0001). The LS mean change in NC score from baseline to Week 24 was -1.25 for the 300 mg q2w dupilumab group (pooled Arm A+B) and -0.38 for the placebo group. The LS mean difference in the dupilumab group versus placebo was -0.87 with 95% CI: -1.03 to -0.71 (p <0.0001).

The secondary endpoints showed similar improvements and support the efficacy of dupilumab compared to placebo. In both studies, dupilumab significantly improved the sense of smell with improvement noted as early as Week 2. Nearly two-thirds of the dupilumab-treated patients who were anosmic at baseline (UPSIT score ≤18) improved their UPSIT score to the non-anosmic range of >19 at Week 24. In the placebo group almost all anosmic patients at baseline remained anosmic.

In study 14146 the follow-up phase showed that the treatment effect in NPS between Week 24 to Week 48 diminished without rebound in the dupilumab group after treatment discontinuation.

3.3. Uncertainties and limitations about favourable effects

The indication granted as an add-on therapy with intranasal corticosteroids adults patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
The long term efficacy is an uncertainty as CRSwNP is a chronic lifelong disease and the current efficacy data remain limited over long term. However, improvement continued in all primary and most secondary endpoints through the end of study treatment (Week 24 for Study EFC 14146 and Week 52 for Study EFC 14280) without reaching a plateau. This suggests that the maximal treatment effect over time has not yet been reached.

3.4. Unfavourable effects

Dupilumab treatment compared to placebo was associated with a higher TEAE incidence 20.0% in the dupilumab group and 16.3% in the placebo group. General disorders and administration site conditions SOC were reported in 14.8% in the dupilumab and 12.1% in the placebo group.
Dupilumab vs. placebo treatment was associated with a higher AESIincidence of Injection site reactions/swelling (serious or severe injection site reactions lasting 24 hours or longer) (13.9% vs. 12.1%) and conjunctivitis Customised MeDDRa Query (CMQ) broad 2.7% vs. 0.4 %).
An increase from baseline in blood eosinophil levels compared to placebo (elevations of eosinophil counts >3.0 Giga/L) was observed in 1.4% vs. 0.4%. Across both pivotal studies through the treatment-emergent period, a total of 12 patients experienced TEAEs in the eosinophilia CMQ. Of which there were 4 SAEs associated with clinical symptoms, two in dupilumab-treated patients (1 EGPA and 1 eosinophilia) and two in placebo (2 EGPA – one patient having received a single dose of dupilumab on day 30). They were also severe,and led to permanent treatment discontinuation in three patients (both dupilumab treated patients and one placebo patient).

Overall, approximately 4% of study subjects in the 24 weeks safety pool receiving dupilumab 300 mg q2w and 2% of those in the placebo groups developed ADA as treatment-emergent response.

Patients treated with dupilumab during the 52-week study EFC14280 showed a treatment-emergent ADA response in 5% and 8%, respectively, depending on the dose regimen (300 mg q2w or 300 mg q2w-q4w). In comparison, patients enrolled in 24 week study EFC14146 (300 mg q2w) developed treatment-emergent ADA response in 15% of all cases vs. 5% noted in the placebo group. Neutralizing antibodies ranged between 2-3% (24 weeks safety pool and 52-week study EFC14280, 300 mg q2w) and 15% (EFC14146). 2 ADA-positive patients in the dupilumab group had treatment period AEs that led to permanent treatment discontinuation and one ADA-positive patient developed an EGPA after one dupilumab administration which consecutively was stopped.

An update of the section 4.4 is introduced to include that cases of vasculitis consistent with EGPA have been reported with both dupilumab and placebo in adult patients with co-morbid asthma in the CRSwNP development program.

Furthermore, data on long-term exposure at the intended dose (300 mg Q2W) are lacking and will be collected in the post approval setting as routine pharmacovigilance.

3.5. Uncertainties and limitations about unfavourable effects

Based on the currently available data, there was no significantly increased risk detectable for dupilumab regarding malignancy, all types of infections or systemic hypersensitivity reactions. However, the safety profile of the CRSwNP population has to be refined over the next years with more data coming from the ongoing open label extension trials in AD and Asthma.

Long-term safety experience is limited in CRSwNP patients as the majority of the safety data (from pooled analysis) comes from 24 weeks of data. The pooled safety data in patients aged > 65 years is rather limited (79 patients) and it appears that older patients have a higher incidence of adverse events than those < 65 years of age in both dupilumab and placebo group. Therefore, older patients may be at a higher risk of adverse events, however as the data set is limited in this population, this remains to be further characterised post approval and no relevant update of the SmPC is necessary at present. The safety of dupilumab use in elderly population will be further monitored through routine pharmacovigilance activities.

3.6. Effects table

Table 1. Effects Table for dupilumab (data cut-off:29 August 2018)

Effect	Short description	Unit %	Treatment DUP 300 mg Q2W	Control PLAC	Uncertainties / Strength of evidence	References
Favourable Effects						
NPS at week 24	Change in NPS from baseline to week 24		-1.79	0.12	(p<0.0001) Clinically meaningful difference	Pooled results from pivotal phase 3 studies (Supporting analyses for summary of clinical efficacy/integrated summary of Effectiveness (ISE))
NC at week 24	Change ion NC from baseline to week24		-1.30	-0.42	(p<0.0001) Clinically meaningful difference	Pooled results from pivotal phase 3 studies (ISE)
UPSIT at week 24	Change in Smell test (UPSIT) at week 24		10.54	-0.03	(p<0.0001) Clinically meaningful difference	Pooled results from pivotal phase 3 studies (ISE)

Effect	Short description	Unit %	Treatment DUP 300 mg Q2W	Control PLAC	Uncertainties / Strength of evidence	References
Snot-22 at week 24	Change in SNOT-22 from baseline to week 24		-29.22	-10.36	(p<0.0001) Clinically meaningful difference	Pooled results from the pivotal phase 3 studies (ISE)
Unfavourable Effects						
TEAE	Injection site reactions	%	3.4	1.8	Most ISR were mild to moderate, only 1 severe ISR	24 weeks PSP
	Arthralgia	%	3.2	1.8	Most reactions were mild to moderate	24 weeks PSP
	Conjunctivitis	%	1.6	0.4	Incidence similar to asthma studies	24 weeks PSP
	Eosinophilia	%	1.1	0	Mainly transient and mild forms; incidence lower than in studied AD and asthma population.	24 weeks PSP
	Insomnia	%	1.4	0	Most reactions were mild to moderate	24 weeks PSP
	Hypertension	%	2.7	1.1	Most reactions were mild to moderate. Evaluation of the HLGT "vascular hypertensive disorders" showed similar frequencies in the dupilumab and placebo group (2.7% and 2.8% respectively)	24 weeks PSP
	ADA response	%	4.3	2.1	ADA were not associated with special TEAE pattern. ADA incidence balanced between treatment groups.	24 weeks PSP

Abbreviations: DUP=Dupilumab, PLAC=Placebo, ISR=Injection Site Reaction, ADA= Anti-drug antibodies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Duplilumab will be used as an add on therapy to intranasal corticosteroids and in patients for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Currently there is still an unmet need for systemic therapies in CRSwNP. Other systemic therapies applied are oral corticosteroids or surgery if the systemic therapy has failed. The multiple side effects of long-term use of systemic corticosteroids are well known and alternative therapeutic options are lacking.

The applicant has demonstrated the beneficial treatment effects of dupilumab 300 mg Q2W as add-on therapy to MFNS in patients with CRSwNP. In both pivotal studies (EFC14146 and EFC14280) statistical significance was reached for the 2 co-primary efficacy endpoints (change from baseline in

NPS and change from baseline in NC score at Week 24) and all multiplicity adjusted key secondary endpoints demonstrating that dupilumab treatment on top of intranasal corticosteroid significantly improved endoscopic, radiologic and clinical measures of CRSwNP compared to intranasal corticosteroid alone. The improvements in efficacy endpoints including patient reported outcomes seen in patients receiving dupilumab are considered clinically meaningful and similar in both pivotal studies. These improvements resulted in significant decrease of systemic steroids use and need for surgery. Additionally, the improvement continued in all primary and most secondary endpoints through the end of study treatment not reaching a plateau. This suggests that the maximal treatment effect over time has not yet been reached.

Intranasal corticosteroids, systemic steroids, and sino-nasal surgery have no meaningful effect on the recovery of sense of smell. In both studies, dupilumab significantly improved the sense of smell.

The general and most relevant safety concerns of dupilumab identified during the CRSwNP program are related to conjunctivitis, injection site reactions, eosinophilia, immunogenicity, limited long term data in patients treated with the proposed (every two-week) Q2W dose of dupilumab as well as uncertainties about the impact of dupilumab on pregnancies and their outcomes.

Conjunctivitis was a rare clinical symptom and incidences were lower than AD program. The long term effect of chronic conjunctivitis in these patients is unknown. Cases of conjunctivitis should continue to be further monitored in the post approval setting in a dedidated study as described in the RMP.

Dupilumab use was not significantly associated with a higher risk of experiencing systemic hypersensitivity reactions in the CRSwNP population since both treatment groups had similar low incidences. This suggests a rather low immunogenic potential of dupilumab in the CRSwNP population; this sort of reaction was mainly locally restricted to injection site reactions. As expected with a biological agent, injection site reactions occurred more frequently in the dupilumab treated populations. One of the events were classified as severe and did not lead to treatment discontinuation. Overall, discontinuation rates due to ISRs were very low. Overall, ISRs seemed to be mild to moderate self-limiting reactions that were well tolerated by patients.

No case of malignancy was present across treatment groups. There is insufficient long term exposure data to characterise long-term safety. This issue has been discussed during the initial MA for AD and is part of the RMP and subject to investigation in the OLE studies.Long-term exposure at the intended dose of dupilumab 300mg Q2W is limited to date.

3.7.2. Balance of benefits and risks

Based on the data provided on efficacy and safety, the therapeutic need of dupilumab in the CRSwNP population is acknowledged and the CHMP is of the opinion that the favourable effects outweigh the unfavourable effects. The benefit-risk balance is principally expected to be the same over the time of treatment.

The approved indication is
Dupixent is indicated as an add-on therapy with intrasanal corticosteroids for the treatment in adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) in patients for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Dupixent is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

As a consequence of this new indication on patients with CRSwNP, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include pharmacological, efficacy and safety data. The Package Leaflet (PL) is updated accordingly.

Additionally minor editorial QRD changes on excipients to the SmPC are introduced in section 6.6 in the 300mg and 200mg strength accordingly. Corresponding changes are implemented in the 200mg strength. Consequently the Annex IIIA is updated.

The variation leads to amendments to the Summary of Product Characteristics , annex IIIA and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

The application is for an extension of indication in patients with severe CRSwNP, who are

As a consequence of this new indication on patients with CRSwNP, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include pharmacological, efficacy and safety data. The Package Leaflet (PL) is updated accordingly.

Additionally minor editorial QRD changes on excipients to the SmPC are introduced in section 6.6 in the 300mg and 200mg strength accordingly. Corresponding changes are implemented in the 200mg strength. Consequently the Annex IIIA is updated.

Summary

Please refer to the assessment report.