15 October 2020
EMA/600660/2020
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Tremfya

International non-proprietary name: guselkumab

Procedure No. EMEA/H/C/004271/II/0017

Marketing authorisation holder (MAH) Janssen-Cilag International N.V.

Note

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

Table of contents

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in DAS28 (CRP)[a,h]			
Subjects evaluable[b]			
N	126	126	128
Mean (SD)	-0.72 (1.015)	-1.44 (1.144)	-1.53 (1.060)
Median	-0.46	-1.36	-1.50
Range	(-4.0; 1.8)	(-4.5; 1.2)	(-4.4; 0.5)
IQ range	(-1.26; 0.00)	(-2.06; -0.61)	(-2.30; -0.76)
All subjects (including those with imputed data)[a,c,h]			
N	126	127	128
Mean (SE)[d]	-0.72 (0.090)	-1.44 (0.101)	-1.53 (0.094)
Model Based Estimates of the Mean Change[a,c,h]			
LSMean (95% CI)[e]	-0.70 (-0.89, -0.51)	-1.43 (-1.61, -1.24)	-1.61 (-1.80, -1.42)
LSMean difference (95% CI)		-0.73 (-0.98, -0.48)	-0.91 (-1.16, -0.66)
p-value[f]		< 0.001	< 0.001

Table 24: Number of Subjects Who Achieved ≥2 Point Improvement from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24, Based on the Composite Estimand; Full Analysis Set 1, Among the Subjects With Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	CNTO1959PSA3001			CNTO1959PSA3002			2-Study Combined		
		Guselkumab			Guselkumab			Guselkumab	
	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline	22	24	18	92	65	82	114	89	100
Subjects evaluable for achieving ≥2 Point Improvement in BASDAI at Week 24[a]	22	24	18	92	65	82	114	89	100
Subjects who achieved ≥2 Point Improvement in BASDAI	4 (18.2%)	14 (58.3%)	10 (55.6%)	29 (31.5%)	35 (53.8%)	49 (59.8%)	33 (28.9%)	49 (55.1%)	59 (59.0%)
95% CI of response rate[b]	(0.0%, 36.6%)	(36.5%, 80.1%)	(29.8%, 81.3%)	(21.5%, 41.6%)	(41.0%, 66.7%)	(48.5%, 71.0%)	(20.2%, 37.7%)	(44.2%, 66.0%)	(48.9%, 69.1%)
Difference (95% CI) in response rates[b]		37.7 (10.9, 64.5)	35.5 (6.2, 64.8)		18.6 (3.1, 34.1)	28.0 (14.1, 41.9)		22.8 (9.4, 36.3)	29.5 (16.7, 42.3)
p-value[c]		0.015	0.035		0.023	< 0.001		0.002	< 0.001

109

Table 24: Number of Subjects Who Achieved ≥2 Point Improvement from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24, Based on the Composite Estimand; Full Analysis Set 1, Among the Subjects With Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	CNTO1959PSA3001			CNTO1959PSA3002			2-Study Combined		
		Guselkumab			Guselkumab			Guselkumab	
	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w
Difference (95% CI) in response rates[d]			-2.8 (-33.0, 27.5)			7.7 (-8.3, 23.6)			4.9 (-9.2, 19.0)
p-value[e]			0.948			0.359			0.438

[a] The estimand is defined as responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed. Subjects with data missing were considered non-responders.
[b] The confidence intervals (CIs) for response rates and for difference in response rates between guselkumab group vs the placebo group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
[c] The p-value comparing the guselkumab group vs the placebo group was based on the CMH test if the Mantel Fleiss criterion was satisfied. Otherwise, the Fisher's exact test was used. The symbol "†" was attached as a superscript to those p-values that were based on the Fisher's exact test.
[d] The confidence intervals (CIs) for difference in response rates between guselkumab 100 mg q4w group vs 100 mg at Weeks 0, 4, and then q8w group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
[e] The p-values comparing between guselkumab 100 mg q4w group vs 100 mg at Weeks 0, 4, and then q8w group were based on the CMH test if the Mantel Fleiss criterion was satisfied. Otherwise, the Fisher's exact test was used. The symbol "†" was attached as a superscript to those p-values that were based on the Fisher's exact test.
The BASDAI is based on 6 questions relating to 5 major symptoms of ankylosing spondylitis through a patient's self assessment. A higher score indicates greater disease severity.

[EMA_TEFBAS05S12.RTF] [CNTO1959\Z_ADHOC_REQ\DBR_PSA_SBLA\RE_EMA_20191223\PROD\EMA_TEFBAS05S12.SAS] 18FEB2020, 13:14

110

List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADR	adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
AUC0-24w	Area under the concentration-time curve to Week 24
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	body mass index
BSA	body surface area
CART	Classification and Regression Tree
CASPAR	Classification criteria for Psoriatic Arthritis
Cave,ss	Average steady-state serum concentration
CCDS	Core Company Data Sheet
CI	confidence interval
CL/F	Apparent clearance
Cmax	Maximum plasma concentration
CRP	C-reactive protein
CSR	clinical study report
Ctrough	Trough concentration
Ctrough,ss	Trough concentration at steady state
Ctrough,wk20	Observed trough serum concentration at Week 20
CYP	cytochrome P450
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS28	Disease Activity Score in 28 joints
DBL	database lock
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying antirheumatic drugs
EC50	Guselkumab exposure at half maximum drug effect
ECLIA	Electrochemiluminescence immunoassay
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EE	Early escape
Emax	Maximum drug effect
EQ-5D	EuroQol-five dimension
E-R	Exposure-response
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
GRACE	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Score
GRAPPA	Group of Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCQ	Hydroxychloroquine
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IgG1λ	Immunoglobulin G1 lambda
IL	Interleukin
ISR	injection-site reaction
ISS	Integrated Summary of Safety
JSN	Joint space narrowing
LEF	Leflunomide
LEI	Leeds Enthesitis Index
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
mCPDAI	Modified Composite Psoriatic Disease Activity Index
MCS	Mental Component Summary
MDA	Minimal disease activity

MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTX	Methotrexate
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMSC	nonmelanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drug
PASDAS	Psoriatic ArthritiS Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PK	Pharmacokinetic
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PT	preferred term
q4w	every 4 weeks
q8w	every 8 weeks
RA	Rheumatoid arthritis
RSE	Relative standard error
SAA	Serum amyloid A
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBAAM	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
SF-36	36-item Short Form Health Survey
SIB	suicidal ideation and behavior
SIR	standard incidence ratio
SMQ	standard MedDRA Query
SMT	Safety Management Team
SOC	system organ class
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of the normal range
URTI	upper respiratory tract infection
US	United States
V/F	Apparent volume of distribution
VAS	visual analogue scale
vdH-S	Van der Heijde-Sharp (score)
VLDA	Very low disease activity
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 11 October 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, II and IIIB

Extension of indication to include a new indication for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. Consequently sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are proposed to be updated. The Package leaflet is proposed to be updated in accordance. Version 5.1 of the RMP has also been submitted. Furthermore, minor QRD changes are introduced in annex II.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0025/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0025/2019 was not yet completed as some measures were deferred.

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 MAH 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 MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Melinda Sobor Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	11 October 2019
Start of procedure:	2 November 2019
CHMP Co-Rapporteur Assessment Report	19 December 2019
CHMP Rapporteur Assessment Report	19 December 2019
PRAC Rapporteur Assessment Report	19 December 2019
PRAC members comments	8 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2020
Request for supplementary information (RSI)	30 January 2020
CHMP Rapporteur Assessment Report	27 May 2020
CHMP Co-Rapporteur Assessment Report	27 May 2020
PRAC Rapporteur Assessment Report	29 May 2020
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	11 June 2020
CHMP members comments	15 and 18 June 2020
Updated CHMP Rapporteur Assessment Report	19 June 2020
2nd Request for supplementary information (RSI)	25 June 2020
CHMP Rapporteur Assessment Report	22 September 2020
CHMP members comments	05 October 2020
Updated CHMP Rapporteur Assessment Report	07 October 2020
CHMP opinion:	15 October 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Claimed therapeutic indication:

Psoriatic arthritis

Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

Epidemiology

Psoriatic arthritis is a chronic inflammatory arthropathy of the peripheral and axial joints associated with psoriasis. The estimated prevalence of PsA in the general population varies from 0.02% to 1.0% across the world; in patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. PsA impacts the joints, bone and cartilage, periarticular tissues (dactylitis), entheses, and skin, and can result in functional disability and impaired quality of life.

Biologic features

The severity of PsA can vary substantially among patients, with some patients developing destructive arthritis leading to bony erosion and loss of joint architecture. In long-term cohort studies of patients with PsA, it has been estimated that approximately 50% to 60% of patients with PsA will not exhibit structural damage over time.

Clinical presentation

Psoriatic arthritis is a chronic inflammatory arthropathy of the peripheral and axial joints associated with psoriasis. The estimated prevalence of PsA in the general population varies from 0.02% to 1.0% across the world; in patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. As a multifaceted disease, PsA impacts the joints, bone and cartilage (progressive structural joint damage), periarticular tissues (dactylitis), entheses, and skin and can result in functional disability and impaired quality of life. The severity of disease can vary substantially among patients, with some patients developing destructive arthritis leading to bony erosion and loss of joint architecture; some patients even require surgical intervention to alleviate pain and restore function of severely damaged joints. In long-term cohort studies of patients with PsA, it has been estimated that approximately 50% to 60% of patients with PsA will not exhibit structural damage over time.

Management

Anti-TNFα agents were the first biologic agents approved for the treatment of PsA. Ustekinumab, an inhibitor of IL-12/23, apremilast, an inhibitor of PDE4, secukinumab and ixekizumab, antibody directed against IL-17, were also recently approved for PsA. These therapies have greatly improved the management of patients with PsA. Unfortunately, 40% to 60% of patients treated with current therapies do not reach a minimal improvement in their joint disease (ie, ACR 20) based on clinical trial data. In addition, TNFi-exposed patients may be more resistant to treatment, as the proportion of subjects achieving an ACR 20 was lower for TNFi-exposed than in TNFi-naive subjects in trials of ustekinumab, apremilast, and secukinumab.

2.1.2. About the product

The mechanism of action of guselkumab is inhibition of IL-23 bioactivity by binding to the p19 subunit of this IL. By binding to the p19 subunit of IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23 mediated intracellular signaling, activation, and

cytokine production.

Guselkumab (Tremfya) has been approved in the EU for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The initial approvals were based primarily on the efficacy, safety, pharmacokinetic, and immunogenicity data from three pivotal Phase 3 studies (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003, hereinafter referred as PSO3001 PSO3002 and PSO3003 studies respectively).

2.1.3. The development programme

The clinical development program for guselkumab in the treatment of adults with active PsA was designed in consideration of the Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Medicinal Products for the Treatment of PsA (CHMP/EWP/438/04, 2006).

The guselkumab clinical development program for PsA includes a completed Phase 2 (CNTO1959PSA2001) and two Phase 3 (CNTO1959PSA3001 and CNTO1959PSA3002 (ongoing)) studies in adult subjects with PsA who had inadequate response to, or were intolerant of conventional therapy (ie, non-biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, or nonsteroidal anti-inflammatory drugs [NSAIDs]), and/or anti-tumor necrosis factor alpha (TNFα) therapies (PSA2001 and PSA3001 only). The guselkumab 100 mg SC at Weeks 0, 4, and every 8 weeks (q8w) thereafter dose regimen was evaluated in study PSA2001. Both the guselkumab q8w and guselkumab SC 100 mg every 4 weeks (q4w) dose regimens were evaluated in studies PSA3001 and PSA3002.

An European Medicines Agency decision (P/0025/2019) was adopted on 22 February 2019, on the agreement of a paediatric investigation plan (EMEA-001523-PIP03-18) and on the granting of a deferral for 5-18 years old children and adolescents with active juvenile psoriatic arthritis (jPsA) and on the granting of a waiver for the paediatric population 0-5 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Guselkumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for guselkumab is required which is acceptable to the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

Guselkumab has been marketed since 13 July 2017 and has received marketing approval for the treatment of adult patients with chronic moderate to severe plaque psoriasis in the United States (US), European Union (EU), and other countries worldwide. The approved dose of guselkumab for the treatment of plaque psoriasis is 100 mg administered subcutaneously (SC) at Week 0, Week 4, and every 8 weeks (q8w) thereafter. This was primarily based on 2 large, Phase 3, placebo-controlled clinical studies

(CNTO1959PSO3001 and CNTO1959PSO3002) in subjects with moderate to severe plaque psoriasis.

The clinical development program for guselkumab in the treatment of active PsA includes a completed Phase 2 global study (CNTO1959PSA2001 [hereafter referred to as PSA2001]) and two Phase 3 global studies (CNTO1959PSA3001 [hereafter referred to as PSA3001] and CNTO1959PSA3002 (ongoing) [hereafter referred to as PSA3002]). The results from the full 1-year dataset from both PsA studies is anticipated post authorisation.

GCP

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

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.

- Tabular overview of clinical studies

Table 5.3.1. 1: Overview of Studies CNTO1959PSA2001, CNTO1959PSA3001, and CNTO1959PSA3002

Design Elements	**CNTO1959PSA2001**	**CNTO1959PSA3001**	**CNTO1959PSA3002**
Study Phase/Type	2/Proof-of-Concept	3/Pivotal	3/Pivotal
All studies were multicenter, randomized, placebo-controlled, double-blind, parallel-group studies			
Study Population	Subjects with active PsA who had inadequate response to or intolerance to previous or current DMARDs and/or NSAIDs. Included 8.7% of subjects previously treated with 1 anti-TNFα agent.	Subjects with active PsA who had inadequate response or intolerance to standard therapies (ie, non-biologic DMARDs, apremilast, or NSAIDs). Included 31.0% of subjects previously treated with up to 2 anti-TNFα agents.	Subjects with active PsA who had inadequate response or intolerance to standard therapies (ie, non-biologic DMARDs, apremilast, or NSAIDs). Subjects were required to be naïve to biologic therapy.
Duration of treatment Follow-up	Last dose at W44 Through W56	Last dose at W48 Through W60	Last dose at W100 Through W112
Subjects treated	149	381	739
Treatment groups (n)	**Group I** (n=100) SC guselkumab 100 mg at W0, 4, 12, 20, 28, 36, and 44 and placebo at W24 **Group II** (n=49) SC placebo at W0, 4, 12, 20, SC guselkumab 100 mg at W24, 28, 36, 44	**Group I** (n=128) SC guselkumab 100 mg q4w from W0 through W48 **Group II** (n=127) SC guselkumab 100 mg at W0 and 4; q8w at W12, 20, 28, 36, and 44; placebo injections at other q8w visits **Group III** (n=126) SC placebo q4w from W0 to W20, crossover to SC guselkumab 100 mg q4w at W24 through W48	**Group I** (n=245) SC guselkumab 100 mg q4w from W0 through W100 **Group II** (n=248) SC guselkumab 100 mg at W0 and 4; q8w at W12, 20, 28, 36, 40, 48 ,56, 64, 72, 80, 88, 96; placebo injections at other q8w visits **Group III** (n=246) SC placebo q4w from W0 to W20, crossover to SC guselkumab 100 mg q4w at W24 through W100
Primary Endpoint	ACR 20 response at W24[a]	ACR 20 response at W24 [a]	ACR 20 response at W24 [a]

Table 5.3.1. 1: Overview of Studies CNTO1959PSA2001, CNTO1959PSA3001, and CNTO1959PSA3002			
Design Elements	**CNTO1959PSA2001**	**CNTO1959PSA3001**	**CNTO1959PSA3002**
Major Secondary Endpoints in order of statistical testing	• PASI 75 response at W24[a] • Change from baseline in HAQ-DI score at W24[a] • ACR 20 response at W16 • ACR 50 response at W24 • Percent improvement in enthesitis score at W24[d] • Percent improvement in dactylitis scores at W24[c]	• IGA response at W24[a,e] • Change from baseline in DAS28 (CRP) at W24[a] • Change from baseline in HAQ-DI score at W24[a] • Change from baseline in SF-36 PCS at W24[a] • ACR 20 response at W16[a] • ACR 50 response at W24[a] • ACR 50 response at W16[a] • ACR 70 response at W24[a] • Resolution of enthesitis at W24[d] • Change from baseline in enthesitis score at W24[d] • Resolution of dactylitis at W24[c] • Change from baseline in dactylitis score at W24[c] • Change from baseline in SF-36 MCS at W24	• IGA response at W24[a,e] • Change from baseline in DAS28 (CRP) at W24[a] • Change from baseline in HAQ-DI score at W24[a] • Change from baseline in vdH-S score at W24[a] • Change from baseline in SF-36 PCS at W24[a] • ACR 20 response at W16[a] • ACR 50 response at W24[a] • ACR 50 response at W16[a] • ACR 70 response at W24[a] • Resolution of dactylitis at W24[a,b,c] • Resolution of enthesitis at W24[a,b,d] • Change from baseline in SF-36 MCS at W24[a] • Change from baseline in dactylitis score at W24[b,c] • Change from baseline in enthesitis score at W24[b,d]

2.3.2. Pharmacokinetics

The PK properties and immunogenicity of guselkumab have been characterized in healthy subjects and in subjects with moderate to severe plaque psoriasis and were presented the initial marketing application for the treatment of psoriasis. In this extension of indication application, information on the PK, pharmacodynamics (PD), and immunogenicity of guselkumab is presented to support the application for the indication for treatment of active PsA.

Phase 2 Study in Subjects with Psoriatic Arthritis (Study PSA2001)

The study is described in detail in the efficacy part of this report (supportive

Pharmacokinetic Summary

For subjects who received 100 mg q8w and did not qualify for EE at Week 16, trough serum guselkumab concentrations reached steady state by Week 20 (median: 0.94 µg/mL; mean±SD: 1.15±0.82 µg/mL) and were maintained through Week 44 (median: 0.89 µg/mL; mean±SD: 1.08±0.78 µg/mL). The trough serum guselkumab concentrations were above quantifiable levels in almost all samples from subjects. Only 1 subject in the guselkumab only group had a trough serum guselkumab concentration at Week 12 that was below the lowest quantifiable concentration (<0.01 µg/mL).

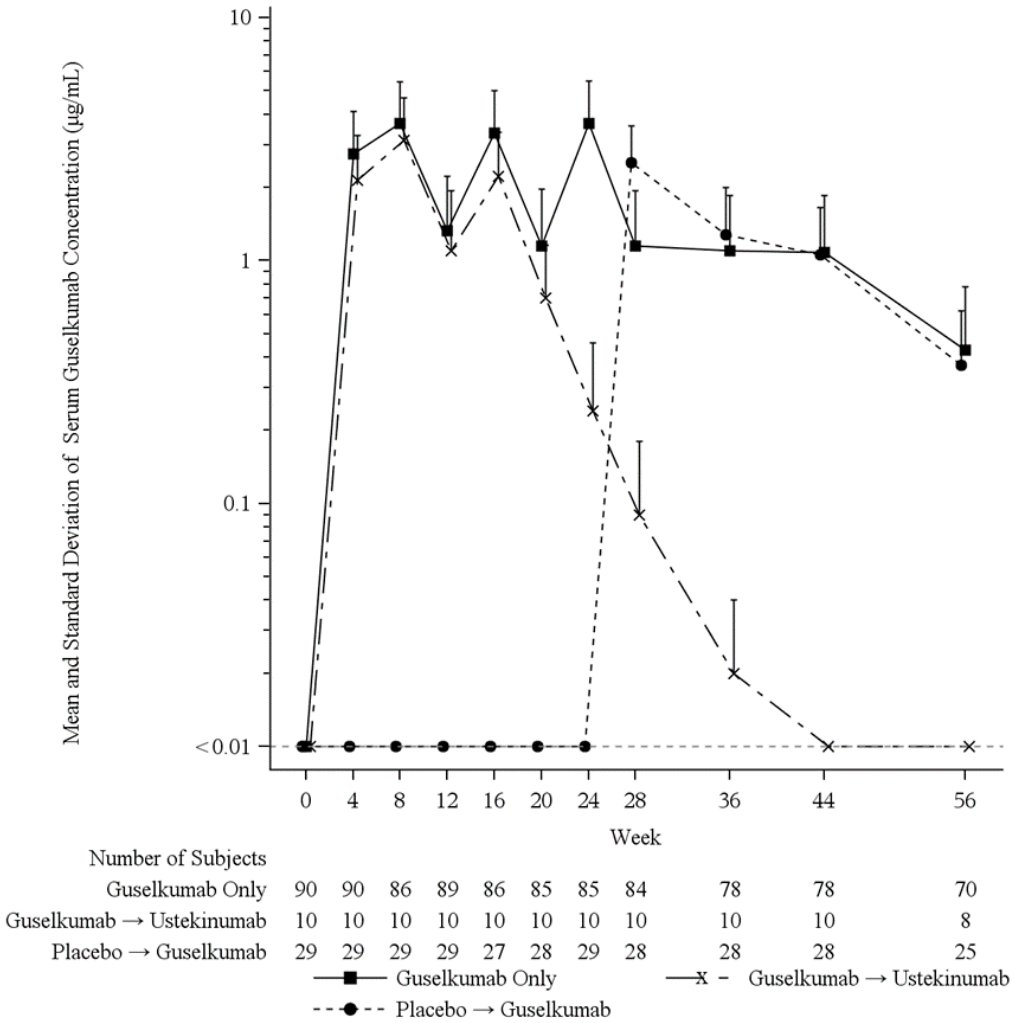
In the guselkumab only group, trough serum guselkumab concentrations appeared to decrease slightly with increasing body weight. Concomitant use of MTX did not have an apparent impact on serum guselkumab concentrations.

Immunogenicity Summary

For subjects who received at least 1 administration of guselkumab and had evaluable serum samples, the incidence of antibodies to guselkumab was 4.7% (6 of 128 subjects) through Week 56 and the highest titer of antibodies to guselkumab was 1:2560.

None of the 6 subjects who were positive for antibodies to guselkumab were positive for NAbs to guselkumab. No apparent difference in mean serum guselkumab concentrations was observed between subjects who were positive and negative for antibodies to guselkumab; however, the number of subjects who were positive for antibodies to guselkumab was very small (n=5 in the guselkumab only group and n=1 in the placebo crossover group) which limits a definitive conclusion

Figure 5.3.2.1: Mean and Standard Deviation of Serum Guselkumab Concentrations (µg/mL) by Visit Through Week 56; Pharmacokinetic Analysis Set (Study PSA2001)



Phase 3 Studies in Subjects with Psoriatic Arthritis

Study PSA3001

Objectives and Study Design are described in the chapter on clinical efficacy of this report

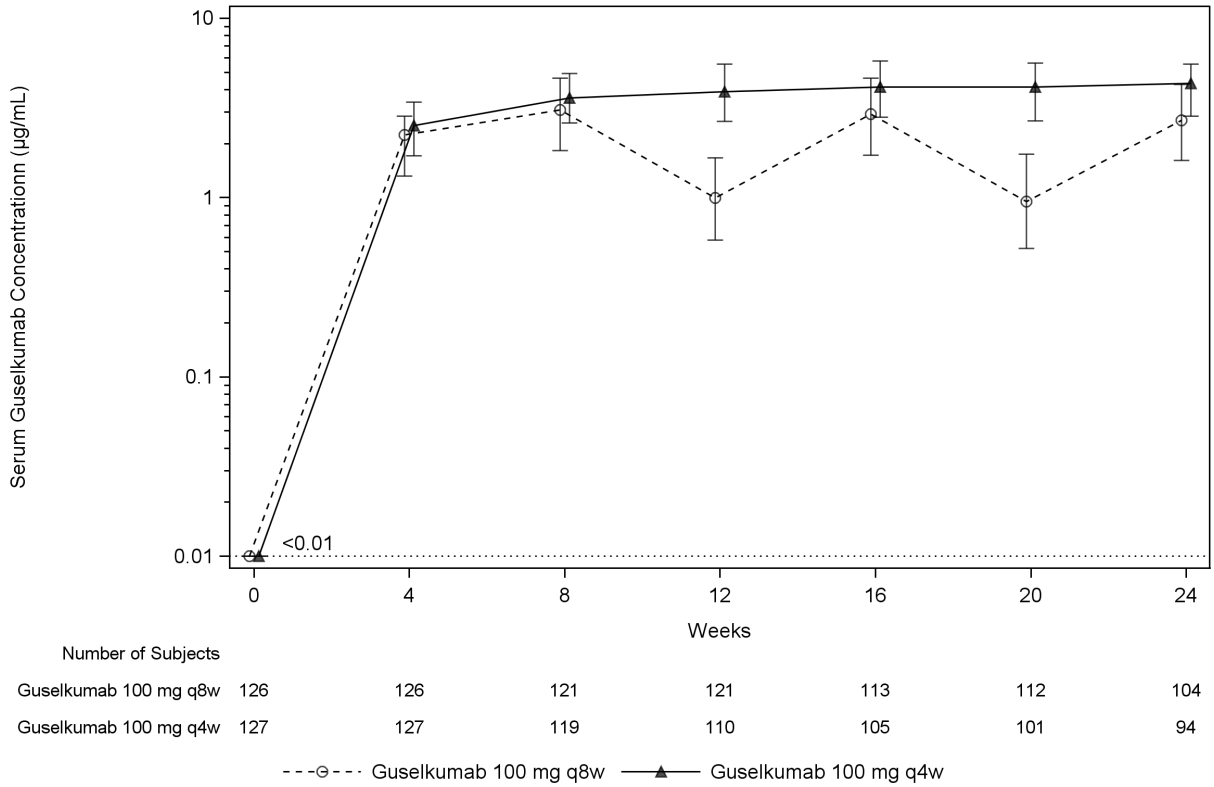
Pharmacokinetic Summary

Following SC administration of guselkumab, trough serum guselkumab concentrations generally reached steady state by Week 20 (median: 0.95 µg/mL; mean±SD: 1.12±0.77 µg/mL) for the 100 mg q8w dose group and by Week 12 (median: 3.90 µg/mL; mean±SD: 4.08±1.88 µg/mL) for the 100 mg q4w dose

group. None of the subjects had trough serum guselkumab concentrations below the lowest quantifiable concentration (<0.01 µg/mL) through Week 24 for both guselkumab dose groups.

Median trough steady-state serum guselkumab concentrations appeared to decrease with increasing body weight. Median trough serum guselkumab concentrations appeared to decrease slightly with increasing CRP levels at baseline. Concomitant use of MTX or non-biologic DMARDs did not have an apparent impact on serum guselkumab concentrations. There was no apparent impact of prior anti-TNFα use on median serum guselkumab concentrations.

Figure 5.3.2.1: Median and Interquartile Range of Serum Guselkumab Concentration (µg/mL) Through Week 24; Pharmacokinetic Analysis Set (Study PSA3001)



[GPK01.RTF] [CNTO1959\PSA3001\DBR_WEEK_24\RE_WEEK_24\PROD\GPK01.SAS] 21MAY2019, 12:33

Immunogenicity Summary

The overall incidence of antibodies to guselkumab through Week 24 was low (2.0%, 5 of 254 subjects) and the highest titer of antibodies to guselkumab was 1:5120. Concomitant use of MTX or non-biologic DMARDs appeared to lower the incidence of antibodies to guselkumab. Prior anti-TNFα use did not have an apparent impact on the incidence of antibodies to guselkumab. However, the small number of subjects who were positive for antibodies to guselkumab limits a definitive conclusion.

One of the 5 subjects (20%) who were positive for antibodies to guselkumab was positive for NAbs to guselkumab.

Median serum guselkumab concentrations tended to be lower in subjects with positive antibodies to guselkumab compared with subjects negative for antibodies to guselkumab. It should be noted that the number of subjects who were positive for antibodies to guselkumab was very small (n=5), which limits a definitive conclusion of the effect of immunogenicity on guselkumab PK.

Study PSA3002

Objectives and Study Design are described in the chapter on clinical efficacy of this report

Pharmacokinetic Summary

Following SC administration of guselkumab, trough serum guselkumab concentrations generally reached steady state by Week 20 (median: 1.05 µg/mL; mean±SD: 1.28±1.03 µg/mL) for the guselkumab 100 mg q8w dose group and by Week 12 (median: 3.35 µg/mL; mean±SD: 3.70±1.92µg/mL) for the 100 mg q4w dose group. The percentage of subjects with serum guselkumab concentrations below the lowest quantifiable concentration (<0.01 µg/mL) at each visit through Week 24 was very low (≤0.5% for the 100 mg q8w group and ≤0.4% for the 100 mg q4w group).

Median trough steady-state serum guselkumab concentrations appeared to decrease with increasing body weight. Median trough serum guselkumab concentrations appeared to decrease slightly with increasing CRP levels at baseline. Concomitant use of MTX or non-biologic DMARDs did not have an apparent impact on serum guselkumab concentrations.

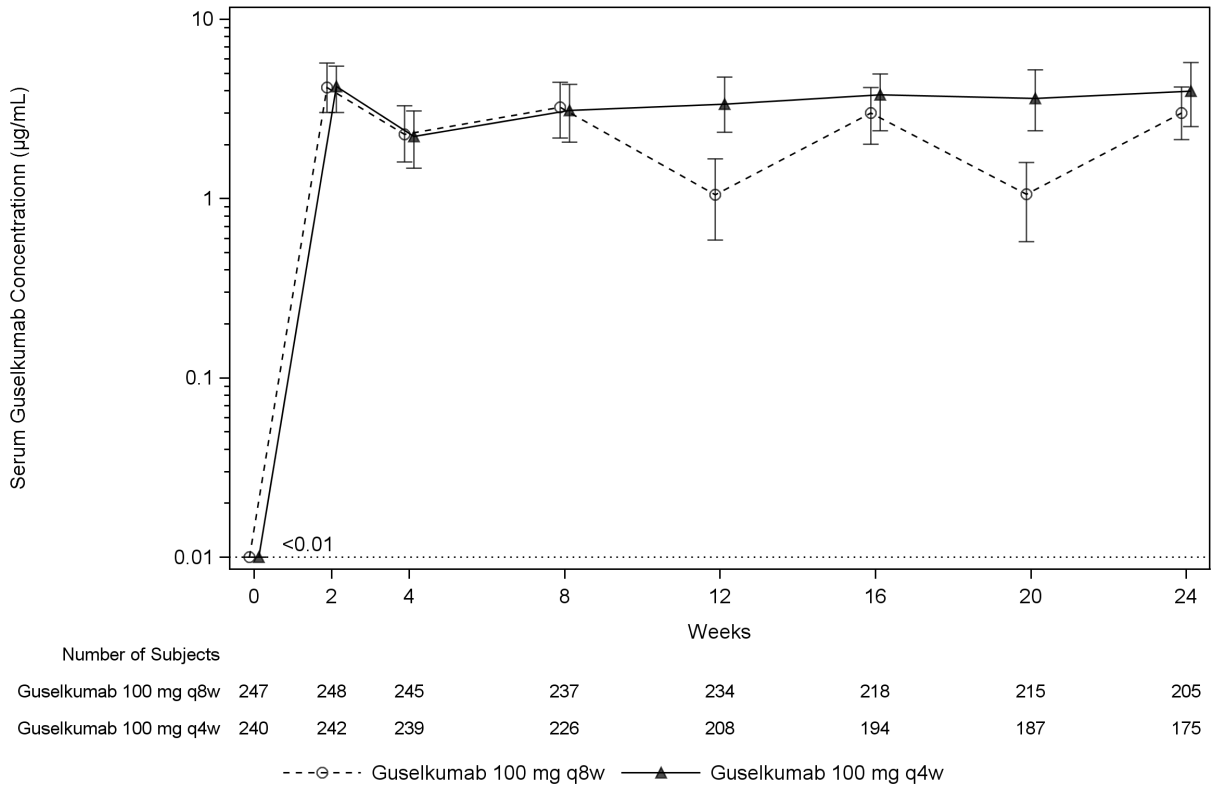
Immunogenicity Summary

The overall incidence of antibodies to guselkumab through Week 24 was low (2.0%, 10 of 490 subjects) and the highest titer of antibodies to guselkumab observed was 1:640. Concomitant use of MTX or non-biologic DMARDs appeared to lower the incidence of antibodies to guselkumab through Week 24. However, the small number of subjects who were positive for antibodies to guselkumab limits a definitive conclusion.

None of the 10 subjects who were positive for antibodies to guselkumab were positive for NAbs to guselkumab.

Median serum guselkumab concentrations tended to be lower in subjects who were positive for antibodies to guselkumab compared with subjects who were negative for antibodies to guselkumab. The small number of subjects who were positive for antibodies to guselkumab (n=10) limits a definitive conclusion of the effect of immunogenicity on guselkumab PK.

Figure 5.3.2.2: Median and Interquartile Range of Serum Guselkumab Concentration (µg/mL) Through Week 24; Pharmacokinetic Analysis Set (Study PSA3002)



[GPK01.RTF] [CNTO1959\PSA3002\DBR_WEEK_24\RE_WEEK_24\PROD\GPK01.SAS] 21MAY2019, 10:39

The measured trough concentrations in the two Phase 3 PsA trials are summarized in Table 5.3.2.1.

Table 5.3.2.2: Summary of Serum Guselkumab Concentrations (µg/mL) Through Week 24 After Multiple 100 mg Subcutaneous Administrations in Subjects with Psoriatic Arthritis; Pharmacokinetic Analysis Set (Studies PSA3001 and PSA3002)

	Guselkumab					
	100 mg w0, 4+q8w			100 mg q4w		
	PSA3001	PSA3002	Combined	PSA3001	PSA3002	Combined
Analysis set: Pharmacokinetic Analysis Set	126	248	374	128	244	372
Week 4[a]						
N	126	245	371	127	239	366
Mean (SD)	2.36 (1.260)	2.51 (1.333)	2.45 (1.309)	2.61 (1.183)	2.39 (1.167)	2.47 (1.175)
Median	2.24	2.29	2.28	2.52	2.22	2.28
Range	(0.2; 6.2)	(0.0; 8.8)	(0.0; 8.8)	(0.3; 5.9)	(0.0; 7.0)	(0.0; 7.0)
IQ range	(1.32; 2.84)	(1.60; 3.30)	(1.50; 3.22)	(1.71; 3.40)	(1.48; 3.08)	(1.56; 3.19)
Week 8[a]						
N	121	237	358	119	226	345
Mean (SD)	3.33 (1.719)	3.52 (1.869)	3.46 (1.819)	3.77 (1.659)	3.32 (1.659)	3.47 (1.670)
Median	3.08	3.22	3.12	3.59	3.10	3.30
Range	(0.6; 9.2)	(0.0; 12.9)	(0.0; 12.9)	(0.4; 9.0)	(0.1; 8.7)	(0.1; 9.0)
IQ range	(1.83; 4.63)	(2.18; 4.44)	(2.09; 4.48)	(2.60; 4.92)	(2.06; 4.33)	(2.18; 4.45)
Week 12[a]						
N	121	234	355	110	208	318
Mean (SD)	1.16 (0.756)	1.28 (1.032)	1.24 (0.948)	4.08 (1.884)	3.70 (1.923)	3.83 (1.915)
Median	1.00	1.05	1.02	3.90	3.35	3.50
Range	(0.1; 3.6)	(0.1; 7.6)	(0.1; 7.6)	(0.5; 9.1)	(0.2; 11.4)	(0.2; 11.4)
IQ range	(0.58; 1.66)	(0.59; 1.67)	(0.58; 1.67)	(2.67; 5.55)	(2.34; 4.76)	(2.42; 4.93)

Week 16[a]						
N	113	218	331	105	194	299
Mean (SD)	3.14 (1.653)	3.29 (1.805)	3.24 (1.753)	4.31 (2.005)	3.99 (2.104)	4.10 (2.072)
Median	2.93	3.00	2.98	4.14	3.79	3.86
Range	(0.5; 8.0)	(0.0; 11.5)	(0.0; 11.5)	(0.3; 10.2)	(0.7; 13.4)	(0.3; 13.4)
IQ range	(1.72; 4.64)	(2.01; 4.17)	(1.91; 4.29)	(2.80; 5.77)	(2.39; 4.95)	(2.52; 5.33)
Week 20[a]						
N	112	215	327	101	187	288
Mean (SD)	1.12 (0.770)	1.22 (0.919)	1.18 (0.871)	4.30 (2.040)	4.06 (2.125)	4.15 (2.095)
Median	0.95	1.05	1.01	4.13	3.63	3.92
Range	(0.1; 3.8)	(0.0; 6.5)	(0.0; 6.5)	(0.5; 11.1)	(0.0; 11.7)	(0.0; 11.7)
IQ range	(0.52; 1.75)	(0.58; 1.59)	(0.53; 1.60)	(2.67; 5.63)	(2.40; 5.22)	(2.48; 5.39)
Week 24[a]						
N	104	205	309	94	175	269
Mean (SD)	3.09 (1.848)	3.36 (1.851)	3.27 (1.852)	4.45 (2.008)	4.19 (2.043)	4.28 (2.031)
Median	2.70	2.99	2.90	4.34	3.98	4.08
Range	(0.4; 11.7)	(0.1; 11.2)	(0.1; 11.7)	(0.5; 10.5)	(0.0; 11.0)	(0.0; 11.0)
IQ range	(1.61; 4.27)	(2.13; 4.18)	(2.00; 4.18)	(2.84; 5.57)	(2.51; 5.74)	(2.72; 5.67)

[a] On study agent injection days, samples for serum guselkumab concentration were taken prior to injection.
IQ=interquartile; q4w=every 4 weeks; q8w=every 8 weeks; SD=standard deviation

[TPK01.RTF] [CNTO1959\Z_SCP\DBR_2019_04\RE_PSA_SBLA\PROD\TPK01.SAS] 21MAY2019, 21:34

Population Pharmacokinetic Analysis

Population PK analysis was performed using pooled data through Week 24 from the 2 Phase 3 studies in subjects with PsA (PSA3001 and PSA3002). The PK sampling schemes for the studies included in the population PK analysis dataset are presented in Table 5.3.3.2

Table 5.3.3.2: Summary of Dose Groups and Pharmacokinetic Sampling Schemes for Studies Included in the Population Pharmacokinetic Analysis

Study Number	SC Guselkumab Treatments	Sampling Time Points[a]
PSA3001	100 mg SC at Weeks 0 and 4 then q8w; 100 mg SC q4w	Weeks 0, 4, 8, 12, 16, 20, 24, and a random day between Week 4 to 12
PSA3002	100 mg SC at Weeks 0 and 4 then q8w; 100 mg SC q4w	Weeks 0, 2, 4, 8, 12, 16, 20, 24, and a random day between Week 4 to 12

The pooled data set comprised 254 subjects from PSA3001 and 492 subjects from PSA3002. A total of 5,626 quantifiable serum guselkumab concentration-time records were included in the population PK analysis. Nine samples (0.16%) were below the limit of quantitation and were excluded from the population PK analysis.

The guselkumab concentration-time profiles in PsA subjects were adequately described by a 1-compartment linear population PK model with first-order absorption and first-order elimination.

A stable covariate model was developed which included the covariate effects of weight, baseline albumin, diabetes, and WBC on CL/F and weight on V/F. Covariates with an effect size of less than 10% including baseline albumin and WBC were removed from the covariate model, resulting in the final population PK model consisting of the effects of body weight on CL/F and V/F and the effects of diabetes on CL/F.

The parameters of the final population PK model are summarized in Table 5.3.2.3.

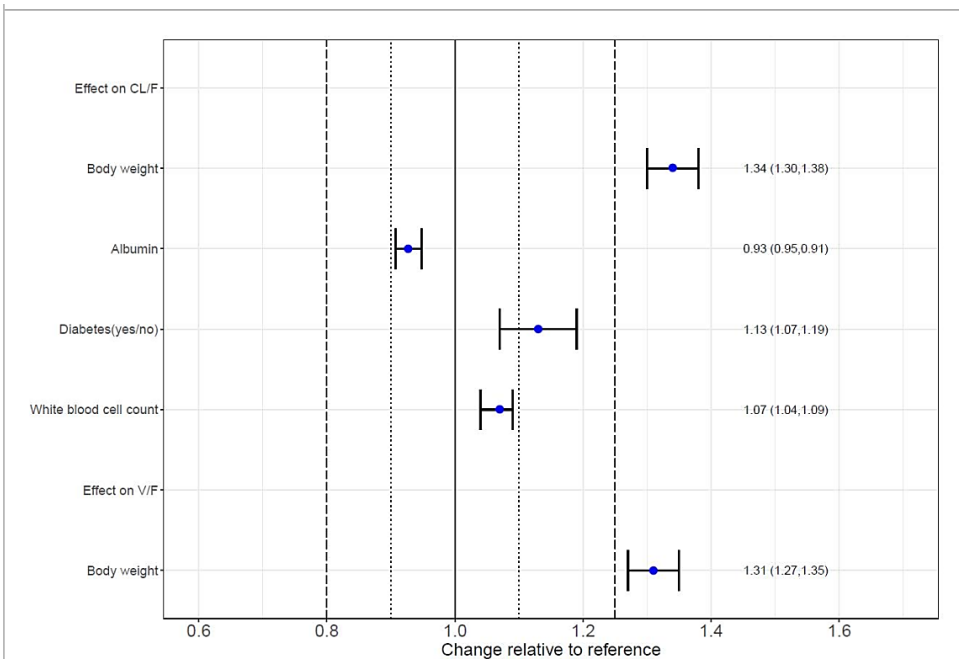
Table 5.3.2.3.: Parameter Estimates in the Final Reduced Population Pharmacokinetic Model

Parameters[a]	**Estimate**[b]	**95% Confidence Interval**	**Magnitude of Change**[c]
CL/F (L/day)[d]	0.596 (1.66)	0.577-0.615	-
Baseline body weight on CL/F	0.926 (7.17)	0.796-1.06	-14.4%-14.5%
Diabetes on CL/F	1.15 (3.54)	1.07-1.23	15%
V/F (L)[e]	15.5 (1.65)	15.0-16.0	-
Baseline body weight on V/F	0.861 (7.65)	0.732-0.990	-13.5%-13.5%
Ka (1/day)	0.572 (8.69)	0.475-0.669	-
IIV of CL/F (%)	38.9 (6.09) [3.51]	36.5-41.2	-
IIV of V/F (%)	33.3 (10.6) [14.3]	29.6-36.6	-
IIV of Ka (%)	93.4 (16.8) [61.7]	76.5-107.7	-
Correlation between IIV of CL/F and V/F	0.101 (8.40)	-	-
Proportional residual error (CV%)	19.1% (2.89)	18.0%-20.2%	-
Additive residual error (µg/mL)	0.00289 (-)	-	-

[a] IIV was calculated as (variance)$^{1/2}$*100%.
[b] Mean (percentage relative standard error [%RSE]) [Shrinkage %] estimates by NONMEM from the final pharmacokinetic dataset.
[c] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, percentage change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population.
[d] $\frac{CL}{F} = 0.596 \times \left(\frac{BWT}{84}\right)^{0.926} \times 1.15^{DIAB}$
[e] $\frac{V}{F} = 15.5 \times \left(\frac{BWT}{84}\right)^{0.861}$
CL/F=apparent clearance; CV%=coefficient of variation; IIV=inter-individual variability; Ka=first-order absorption rate constant; V/F=apparent volume of distribution
Source: Mod5.3.3.5/PopPKReport/PSA/Tab7

The impact of the covariates on the respective PK parameters in the covariate model after backward elimination is illustrated in a forest plot (Figure 5.3.2.4).

Figure 5.3.2.4: Effects of Covariates on CL/F and V/F from the Covariate Model (Run 50)



Effects of covariates were assessed using the stable covariate model. The effect sizes for discrete covariates (less common category/the most common category) were the parameter estimates of the less common category relative to the most common category. The effect size for continuous covariates (covariate values at 75th percentile/covariate values at 25th percentile) were calculated as the ratio of E75/E25, where E75 and E25 were PK parameter values with covariate values at 75th percentile and 25th percentile of the population respectively. Blue points represent model predictions and black line segments are the corresponding 90% confidence intervals. The associated values are shown on the right column. The gray long-dash and dotted vertical lines are the 80% to 125% and the 90% to 110% boundaries.

Covariate effects by simulations

The model-predicted median Ctrough,ss and AUCτ of guselkumab in PsA subjects with a body weight ≥90 kg were about 33.4% and 28.8% lower than in subjects <90 kg, respectively, at 100 mg q8w. The model-predicted median Ctrough,ss and AUCτ of guselkumab in PsA subjects with a body weight ≥90 kg were about 30.4% and 28.8% lower than in subjects <90 kg, respectively, at 100 mg q4w.

The model-predicted median Ctrough,ss and AUCτ of guselkumab in subjects with diabetic comorbidity were approximately 30.3% and 18.9% lower than in subjects without diabetic comorbidity, respectively, at 100 mg q8w. The model predicted median Ctrough,ss and AUCτ of guselkumab in subjects with diabetic comorbidity were approximately 22.6% and 18.9% lower than in subjects without diabetic comorbidity, respectively, at 100 mg q4w.

Table 5.3.2.5: Simulated Guselkumab Steady-State Trough Concentration (Ctrough,ss) and Area under the Curve during One Dosing Interval (AUC $_{\tau}$) grouped by Body Weight (<90 kg versus ⩾90 kg) and Diabetic Comorbidity Following Guselkumab 100 mg q8w and 100 mg q4w

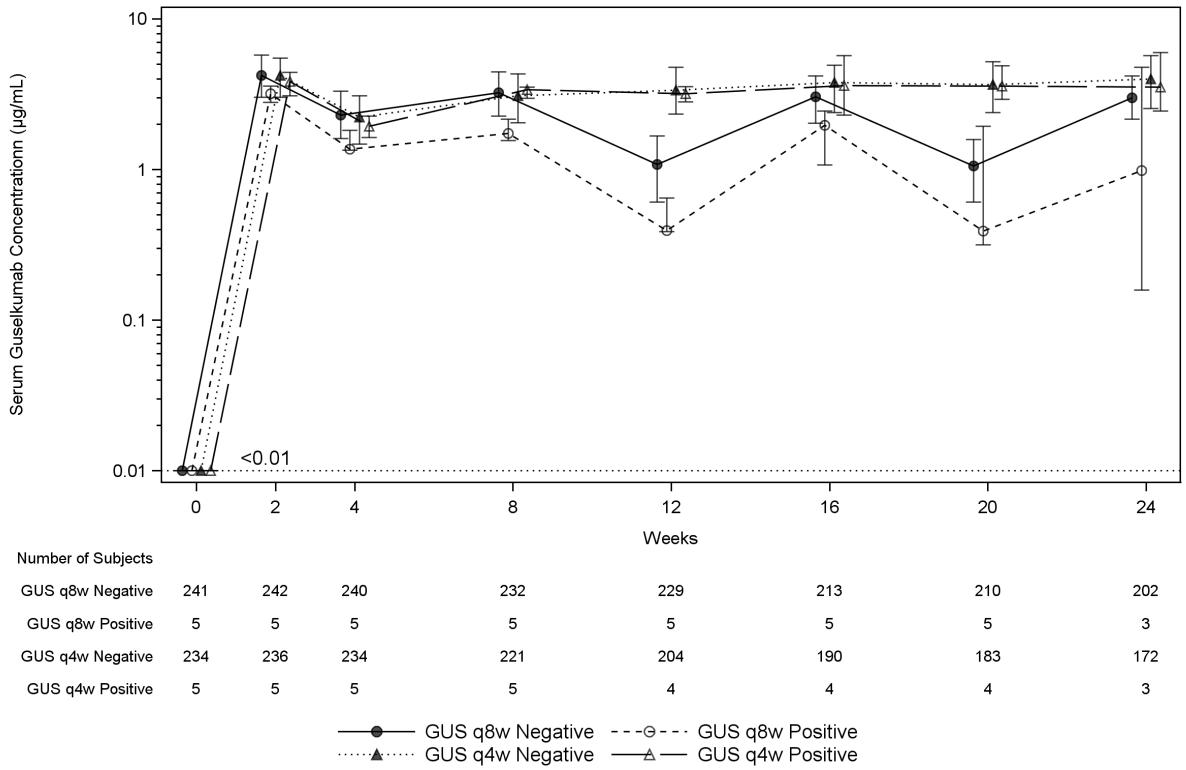
PK Parameter	Group	Number of Subject	Mean	Median	5^{th}-95^{th} Percentiles
100 mg q8w					
$AUC_{0\text{-}w8,ss}$ (µg/mL×d)	weight<90kg	3021	209	191	96.9-389
	weight≥90kg	1979	147	136	71.3-265
	non-diabetes	4561	188	169	83-359
	diabetes	439	151	137	70.3-274
$C_{trough,ss}$ (µg/mL)	weight<90kg	3021	1.27	1.08	0.318-2.87
	weight≥90kg	1979	0.864	0.719	0.215-2.01
	non-diabetes	4561	1.14	0.94	0.277-2.68
	diabetes	439	0.773	0.655	0.182-1.71
100 mg q4w					
$AUC_{0\text{-}w4,ss}$ (µg/mL×d)	weight<90kg	3021	209	191	96.9 - 389
	weight≥90kg	1979	147	136	71.3 - 265
	non-diabetes	4561	188	169	83-359
	diabetes	439	151	137	70.3-274
$C_{trough,ss}$ (µg/mL)	weight<90kg	3021	4.7	4.18	1.79-9.39
	weight≥90kg	1979	3.25	2.91	1.22-6.48
	non-diabetes	4561	4.22	3.68	1.52-8.64
	diabetes	439	3.17	2.85	1.18-6.28

Simulations were based on final reduced population PK model (n=5000).
Key: $AUC_{0\text{-}w4,ss}$=Area under the curve from 0 to 4 weeks at steady state; $AUC_{0\text{-}w8,ss}$=Area under the curve from 0 to 8 weeks at steady state; $C_{trough,ss}$=Trough concentration at steady state; q4w= every 4 weeks; q8w= every 8 weeks

Antibodies to Guselkumab and Pharmacokinetics

In the population PK covariate analysis, the presence of antibodies and the impact of antibodies to guselkumab as a time-varying variable did not have an apparent effect on the CL/F of guselkumab. The small number of subjects who were positive for antibodies to guselkumab (total n=15) limited to draw definitive conclusion of the effect of immunogenicity on guselkumab PK. In study PSA3001 only 1 subject was positive for antibodies to guselkumab but in study PSA3002, in the guselkumab 100 mg q8w group, median serum guselkumab concentrations seems to be lower in subjects who were positive for antibodies to guselkumab compared with subjects who were negative. At same time, in the 100 mg q4w group, such difference cannot be observed. (Figure 5.3.2.5).

Figure 5.3.2.5: Median and Interquartile Range of Serum Guselkumab Concentrations (µg/mL) Through Week 24 by Antibody Status; Immunogenicity Analysis Set (Study PSA3002)



Absorption

The mean absolute bioavailability (F) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6%, 48.7%, and 54.9%, respectively, for lyophilized formulation, liquid formulation in PFS-U, and liquid formulation in PFS-FID.

Distribution

The population estimate for apparent volume of distribution (V/F) is 15.5 L. This value is very close what was obtained in RA patients (13.5L)

Elimination

The population estimate for r apparent clearance (CL/F) is 0.596 L/day. This value is very close to what was obtained in RA patients (0.516 L/day)

Dose proportionality and time dependencies

There is no new data in this regard. This was considered acceptable by the CHMP.

Special populations

Of the 746 psoriatic arthritis patients exposed to guselkumab in phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. No consistent

differences were observed in the overall safety profile of guselkumab among age subgroups through Week 24 and the data cut (please refer to assessment of clinical safety).

Pharmacokinetic interaction studies

There is no new data in this regard. This was considered acceptable by the CHMP.

Pharmacokinetics using human biomaterials

There is no new data in this regard. This was considered acceptable by the CHMP.

2.3.3. Pharmacodynamics

Mechanism of action

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high affinity. By binding to the p19 subunit of IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23 mediated intracellular signaling, activation, and cytokine production.

Primary and secondary pharmacology

Biomarkers

Clinical characteristics at baseline

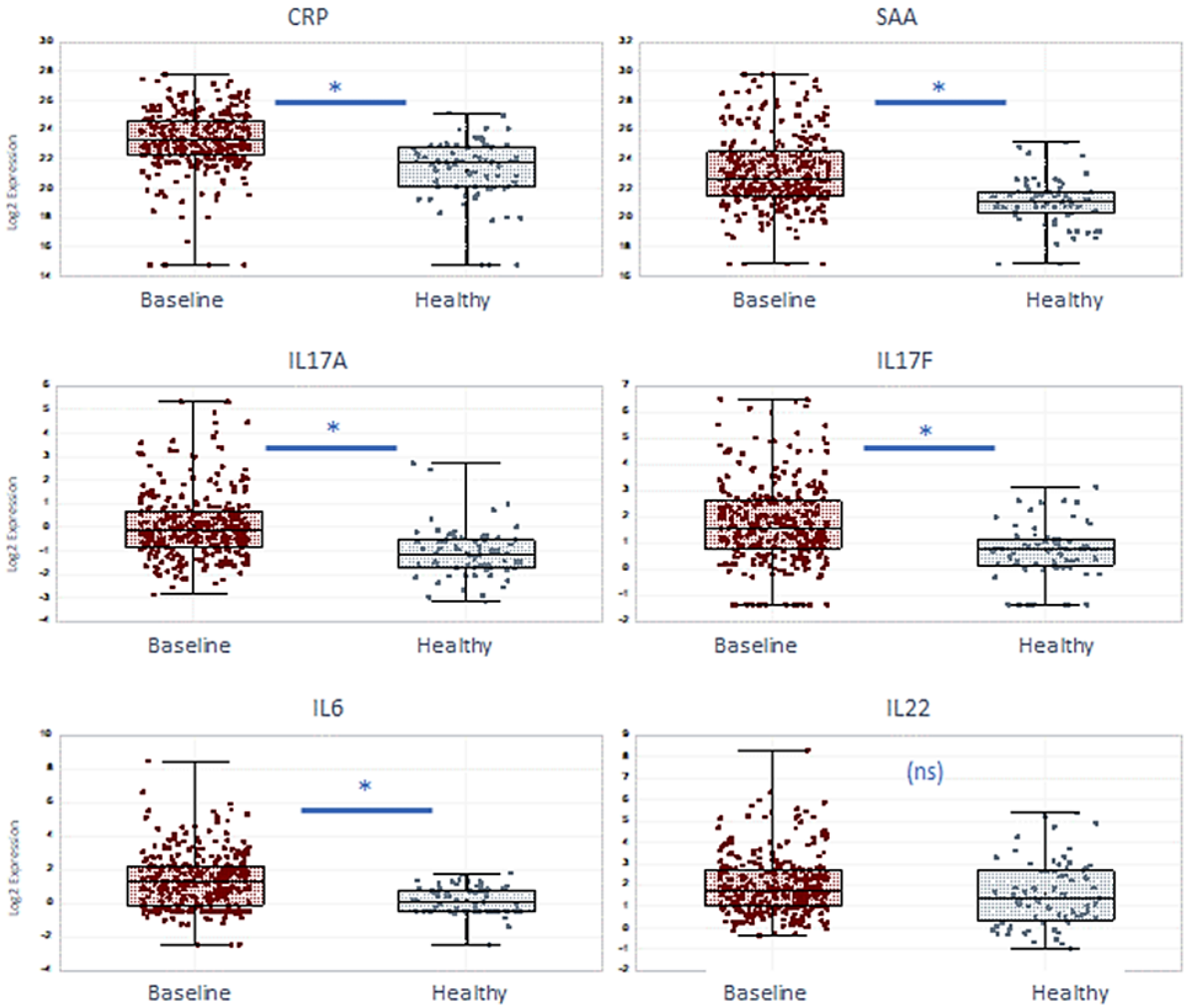
In PSA3001 and PSA3002, 21 serum proteins were measured from a subpopulation of 50 subjects per treatment group per study (n=300 subjects in total) at Weeks 0 (pretreatment), 4, and 24. Additionally, serum samples were evaluated from 34 healthy control subjects procured independently of these studies. The control subjects were selected to reflect the demographics of the PsA studies (age, sex, and race/ethnicity).

At baseline, serum levels of acute phase proteins CRP, serum amyloid A (SAA), and IL-6, and Th17 effector cytokines IL-17A and IL-17F were elevated in PsA study subjects compared with healthy control subjects in both studies (Figure 5.3.3.1) There was no significant dysregulation in soluble ICAM-1, soluble VCAM-1, CCL2 (MCP-1), CCL22 (MDC), CCL4 (MIP-1-β), IFN-γ, IL-8, TNFα, YKL-40, or IL-22 in PsA subjects compared with healthy subjects. Effector cytokines associated with the IL-23/Th-17 (IL-17A, IL-17F, and IL-22) and inflammatory protein CCL22 were significantly correlated with baseline psoriasis disease activity, including BSA and PASI (Spearman Signed Rank $p<0.05$ and $r>0.25$). Acute phase proteins CRP, SAA, and IL-6 and inflammatory protein YKL40 were significantly associated with baseline joint disease as measured by DAS28 (CRP) (Spearman Signed Rank $p<0.05$ and $r>0.25$).

The PSA3001 study included subjects previously treated with one or more biologic anti-TNF agent. This subpopulation of subjects had significantly higher levels of SAA, IL-6, IL-17A, and IL-17F compared with subjects in PSA3001 without prior exposure to anti-TNF agents ($p<0.05$ and geometric mean ≥40% higher), although these proteins were significantly up-regulated compared with the healthy control set for both groups.

There was so significant difference in baseline serum biomarkers between subjects with or without baseline methotrexate usage (MTX)

Figure 5.3.3.1: Biomarkers Associated with Psoriatic Arthritis at Baseline

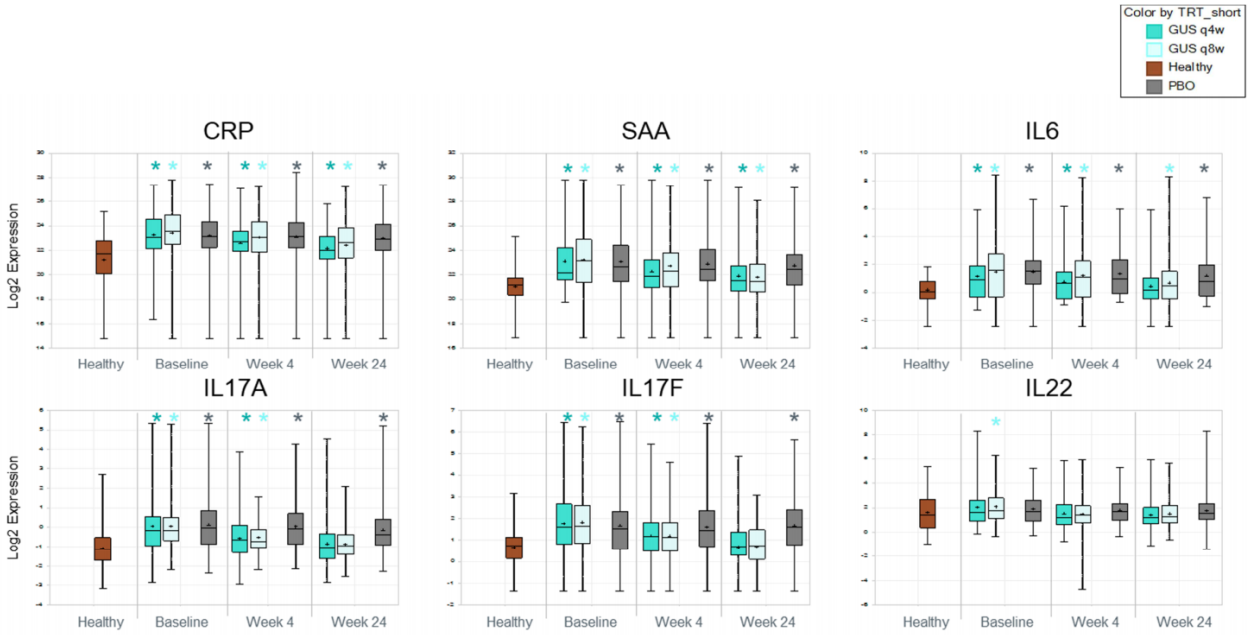


Concentration (y-axis, log2) of analyte (indicated at top of plot) for healthy control subjects and subjects with psoriatic arthritis (baseline), indicated on x axis. *GLM p<0.05 and absolute value of fold difference ≥1.4 versus healthy control subjects. Data presented as symbols represent individual subjects and summarized by box (inter-quartile range and median) and whiskers (range). CRP=C-reactive protein; IL=interleukin; SAA=serum amyloid A
Source: Mod5.3.4.2/BiomarkerExploratoryReport/Fig2

Guselkumab effect on biomarkers

A strong pharmacodynamic effect was observed with both 100mg q4w and 100mg q8w dosing regimens of guselkumab (Figures 5.3.3.2). Guselkumab treatment decreased levels of acute phase proteins CRP, SAA and IL-6, and Th17 effector cytokines IL-17A, IL-17F and IL-22 within 4 weeks of initiation of treatment. Guselkumab treatment further reduced levels by week 24, and to a greater extent than observed with placebo. In guselkumab treated subjects at week 24, serum IL-17A and IL-17F levels were not significantly different from those observed in a demographically matched healthy cohort (Figure 5.3.3.2). IL-6 is only reduced to healthy levels by the guselkumab q4w dose at Week 24, though the trend was similar for the q8w dose as well (p=0.0405, fold difference= 1.4).

Figure 5.3.3.2: Post-baseline Serum Protein Levels Compared to Healthy



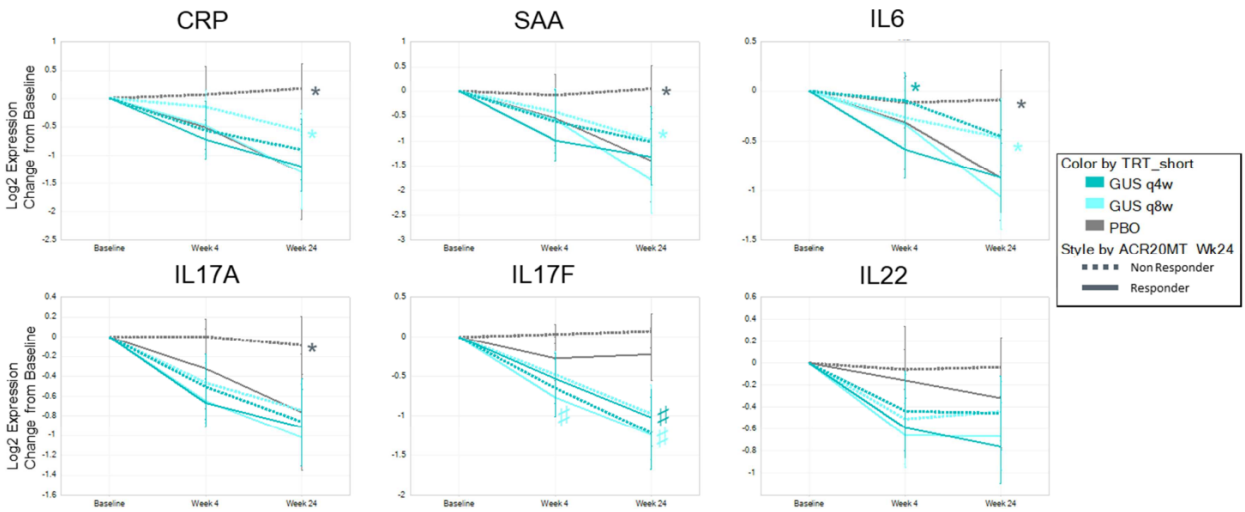
- indicates statistically significant difference vs Healthy p<.05 and |fold difference| ≥ 1.4.

Association of biomarkers with the clinical response

ACR20

Baseline serum proteins were not associated with ACR20 response to guselkumab at week 24. (Figure 5.3.3.3)

Figure 5.3.3.3: Change from Baseline in Serum Proteins After Guselkumab Treatment stratified by the ACR 20 response

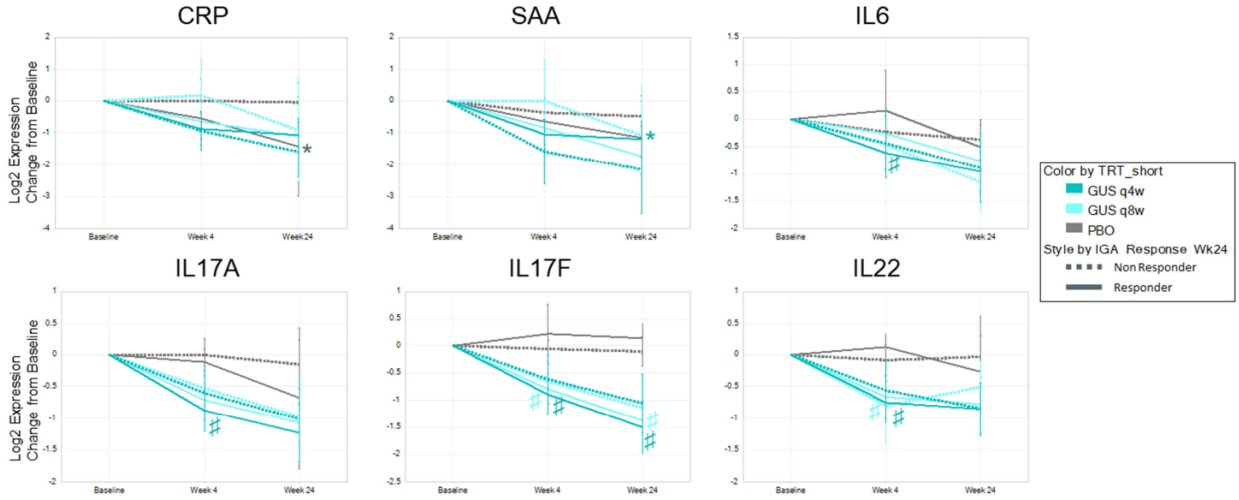


* indicates statistical significant difference R vs NR p<.05 and |fold difference| ≥ 1.4; ♯ indicates statistical significant difference PBO R vs Trt R defined by p <.05 and |fold difference| ≥ 1.4; Error bars represented 2 SEM (approximately 95% CI)

IGA

In the subset of subjects who met the clinical analysis criteria for IGA response assessment (n=151), all cytokines evaluated were not significantly associated with IGA response to guselkumab.(Figure 5.3.3.4)

Figure 5.3.3.4: Change from Baseline in Serum Proteins After Guselkumab Treatment stratified by the IGA response

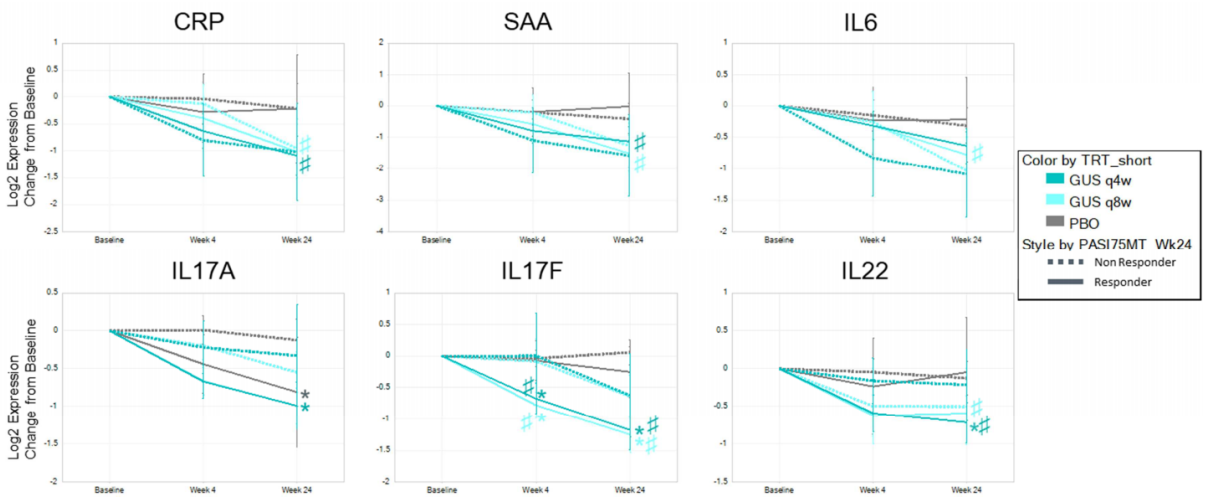


* indicates statistical significant difference R vs NR p<.05 and |fold difference| ≥ 1.4; ♯ indicates statisticalsignificant difference placebo R vs guselkumab R defined by p <.05 and |fold difference| ≥ 1.4; Error bars represented 2 SEM (approximately 95% CI) IGA: investigator's global assessment

PASI75

IL-17F levels were decreased with guselkumab treatment in both dose groups and were reduced to a greater extent in PASI75 responders compared to PASI75 non-responders (Figure 5.3.3.5) This difference was not observed in the placebo arm. While CRP and SAA were decreased in the guselkumab arms and not in the placebo arm, a difference was not observed between PASI75 clinical responders compared to non-responders.

Figure 5.3.3.5: Change From Baseline Association With Week 24 Stratified by PASI75 response



2.3.4. PK/PD modelling

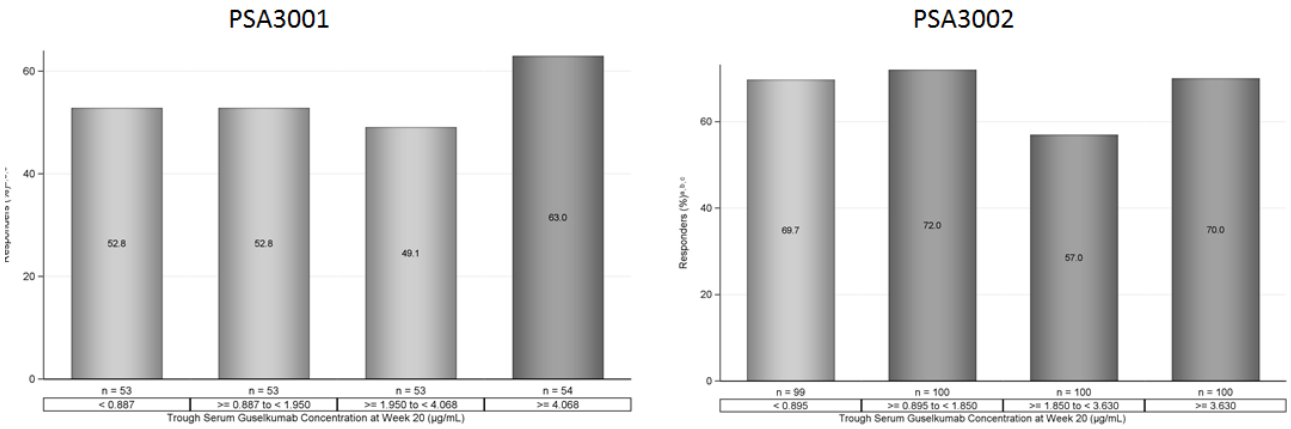
Exposure-response Analyses in Subjects with Psoriatic Arthritis

The E-R relationships between trough serum guselkumab concentration and selected efficacy endpoints were assessed for each individual Phase 3 PsA study. Clinical efficacy data including ACR 20 and ACR 50 at Week 24, change from baseline in DAS28 (CRP) at Week 24 and IGA response at Week 24 were used in the E-R analyses because these were either the primary or major secondary endpoints in both studies. In addition, clinical responses measured by these endpoints at Week 20 were also used in the E-R analyses because Week 20 matched the time of steady-state trough concentrations for both dose regimens. The steady-state trough serum guselkumab concentrations from both dose groups at Week 20 were divided into 4 groups based on quartiles with approximately equal numbers of subjects in each group for each dose group.

ACR20 response and Trough Serum Guselkumab Concentrations

There appeared to be a weak E-R relationship for ACR 20 response rate at Week 20 by trough guselkumab concentration quartiles at Week 20 in PSA3001, while no apparent E-R relationship was observed for ACR 20 response rate at Week 20 in PSA3002. (Figures 5.3.4.1)

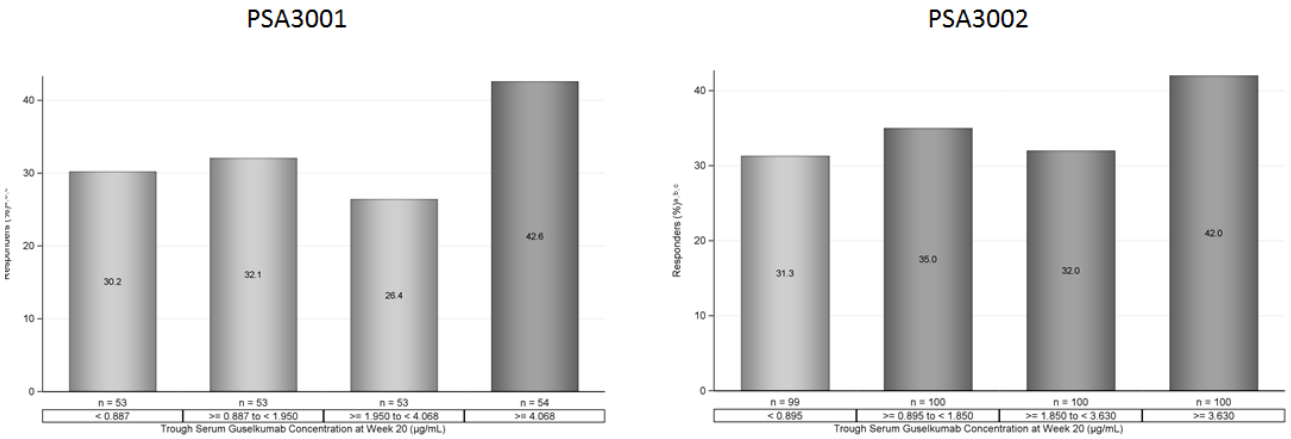
Figure 5.3.4.1: Proportion of Subjects Who Achieved an ACR 20 Response (Composite Estimand) at Week 24 by Trough Serum Guselkumab Concentrations (Quartiles); Pharmacokinetic Analysis Set (Studies PSA3001 and PSA3002)



ACR50 response and Trough Serum Guselkumab Concentrations

A weak E-R relationship was observed for the ACR 50 response rate at Week 20 by trough guselkumab concentration quartiles at Week 20 in PSA3002, while no apparent E-R relationship was observed for the ACR 50 response rate at Week 20 in PSA3001.

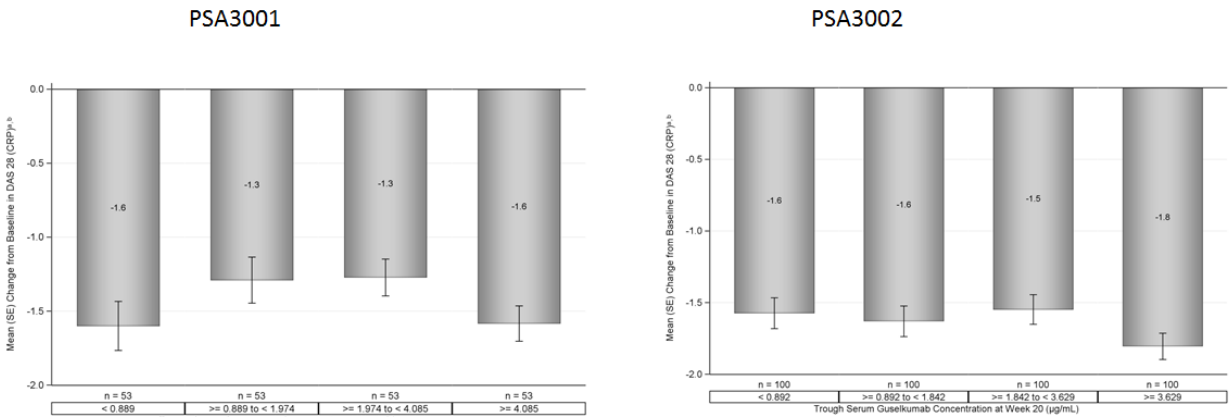
Figure 5.3.4.2: Proportion of Subjects Who Achieved an ACR 20 Response (Composite Estimand) at Week 24 by Trough Serum Guselkumab Concentrations (Quartiles); Pharmacokinetic Analysis Set (Studies PSA3001 and PSA3002)



DAS28 (CRP) response and Trough Serum Guselkumab Concentrations

In both PSA3001 and PSA3002, there were no apparent E-R relationships for mean changes from baseline in DAS28 (CRP) at Weeks 20 or 24 by steady-state trough guselkumab concentration quartiles at Week 20

Figure 5.3.4.3: Mean (SE) Change from Baseline in DAS 28 (CRP) (Composite Estimand) at Week 24 by Trough Serum Guselkumab (Combined) Concentrations (Quartiles) at Week 20; PK Analysis Set (Study CNTO1959PSA3001)

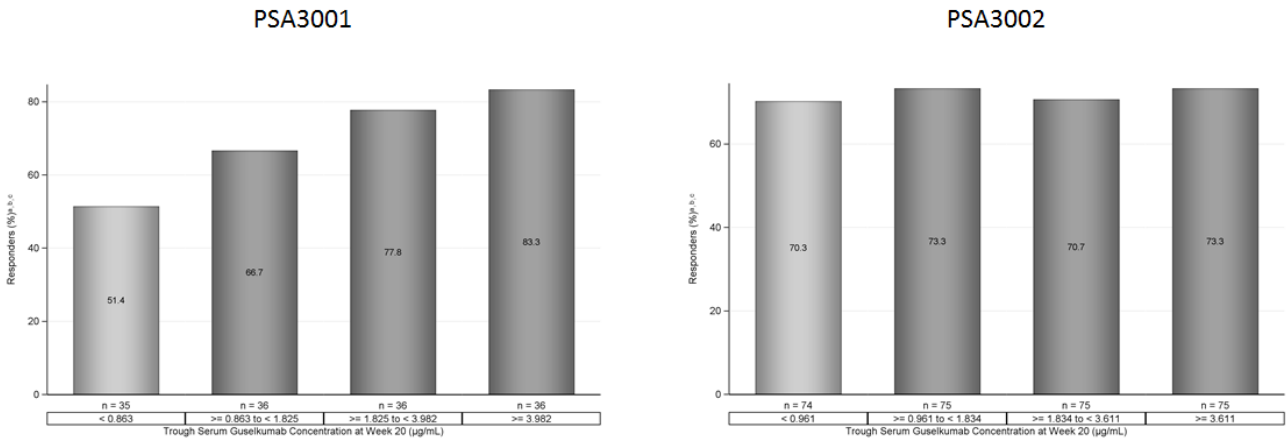


Source: Mod5.3.5.1/PSA3001/W24CSR/Sec6.5.2 and Mod5.3.5.1/PSA3002/W24CSR/Sec6.5.2).

IGA Response and Trough Serum Guselkumab Concentrations

Only subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 at baseline were used in this analysis. For the major secondary endpoint of IGA response (ie, an IGA psoriasis score of 0 [cleared] or 1 [minimal] and ≥2-grade reduction from baseline) at Week 24 by steady-state trough guselkumab concentration quartiles at Week 20, an apparent E-R relationship was observed in subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 at baseline in PSA3001, while no apparent E-R relationship for IGA response was observed in PSA3002.

Figure 5.3.4.4: Proportion of Subjects Who Achieved IGA Response (Composite Estimand) at Week 24 by Trough Serum Guselkumab Concentrations (Quartiles); Pharmacokinetic Analysis Set Among the Subjects with ≥3% BSA Psoriatic Involvement and an IGA score of ≥2 (mild) at Baseline (Studies PSA3001 and PSA3002)



Source: Mod5.3.5.1/PSA3001/W24CSR/Sec6.5.3 and Mod5.3.5.1/PSA3002/W24CSR/Sec6.5.3

Exposure-response modelling

Data from a total of 1,120 subjects in the 2 Phase 3 studies (PSA3001 and PSA3002) were included in the final dataset for the E-R modelling analyses.

Method

Data from 1,120 subjects were included in the final dataset for the E-R analyses. Analyses were conducted using a landmark analysis approach, which used ordinal logistic regression to correlate American College of Rheumatology (ACR) or the Investigator's Global Assessment (IGA) responses at Week 20 and Week 24 with guselkumab pharmacokinetic (PK) exposure metrics. These metrics included model-predicted cumulative area under the concentration-time curve (AUC) from Week 0 to Week 24 (AUC0-24w), model-predicted average concentration at steady state ($Cave_{ss}$), and observed trough serum concentration at Week 20 (Ctrough,wk20). The probability of achieving 20%, 50%, or 70% improvement in arthritis activity relative to baseline (ACR20, ACR50, or ACR70) was simultaneously modelled by re-parametrizing the ACR response to 1 ordered categorical variable with 4 possible outcomes (=0 if ACR70 achieved; =1 if ACR50 achieved, but not ACR70; =2 if ACR20 achieved, but not ACR50; =3 if ACR20 not achieved). The probability of achieving Investigator's Global Assessment score of cleared (0) or minimal (1) (IGA0/1; IGA≤1) and Investigator's Global Assessment score of cleared (0) (IGA0; IGA=0) was also simultaneously modelled by re-parametrizing the IGA response to 1 ordered categorical variable with 3 possible outcomes (=0 if IGA score =0; =1 if IGA score =1; =2 if IGA score >1). Subjects with a baseline IGA score of ≤1 were excluded from IGA analyses.

Based on graphical exploration, logistic regression models, which assumed a maximum drug effect (Emax) relationship between PK exposure metrics and efficacy response rates, were used for the landmark analysis base models. Covariate models were then developed through a standard Stepwise Covariate Modelling (SCM) development approach. The covariates tested included body weight [BWT], diabetes comorbidity status [DIAB], baseline disease characteristics (ie, baseline C-reactive protein [BCRP], baseline Disease Activity Score in 28 joints (DAS28) [BDAS], baseline IGA score [BIGA], baseline Psoriasis Area and Severity
Index (PASI) score [BPAS], disease duration [DDUR]), prior anti-TNFα treatment [TNFT], and concomitant medications (ie, methotrexate [MTX], disease-modifying antirheumatic drugs other than methotrexate [DMAR2], corticosteroid [CORT], and nonsteroidal anti-inflammatory drugs [NSAD]). Covariate searches were performed on the intercept (clinical response in the absence of drug exposure), the guselkumab exposure at half maximum drug effect (EC50), and Emax. Model performance was evaluated by goodness-of-fit plots, generated by overlaying the observed and model-predicted

probabilities of achieving a given efficacy outcome.
Simulations were conducted to predict ACR20/50/70, IGA0/1, and IGA0 responses to the 2 different dose regimens (100 mg q8w and 100 mg q4w) using the final E-R models. The simulated results were stratified by the covariates in the final models, and parameter uncertainties were included in the simulations to produce 90% confidence intervals (CIs) for the predicted responses.

Results

Logistic regression models, assuming an Emax relationship between the PK exposure metrics and efficacy response rates, adequately described the observed data, as indicated by goodness-of-fit plots. For the 3 E-R models of the ACR20/50/70 responses using different exposure metrics (AUC0-24w, $Cave_{ss}$, and Ctrough,wk20), the baseline DAS28 score was identified as a covariate based on Emax, with a trend indicating that subjects with lower baseline DAS28 scores had higher ACR20/50/70 responses. The baseline PASI score was also identified as a covariate on Emax for 2 landmark models (using $Cave_{ss}$ and Ctrough,wk20 as exposure metrics); subjects with higher baseline PASI scores tended to have higher ACR20/50/70 responses. The parameter estimates from the final E-R models for ACR20/50/70 responses are summarized in Table 5.3.4.1.

Table 5.3.4.1: Parameter Estimates of Exposure-response Models for ACR 20/50/70 Responses at Week 20 or Week 24

Parameters	**Week 24 using AUC_{0-24w}[a]**	**Week 24 using $C_{ave,ss}$[a]**	**Week 20 using $C_{trough,wk20}$[a]**
Run#	102	202	302
β_1	-1.94 (6.62)	-1.92 (6.74)	-1.86 (6.94)
d_2	1.23 (5.35)	1.23 (5.45)	1.15 (6.02)
d_0	0.979 (7.64)	1.00 (7.66)	1.09 (7.77)
E_{max}	1.44 (19.7)	1.53 (18.2)	1.26 (12.9)
BDAS on E_{max}	-0.847 (27.1)	-0.827 (27.5)	-0.981 (21.5)
BPAS on E_{max}	-	0.142 (35.9)	0.169 (30.2)
EC_{50}	134 (127)	1.06 (100)	0.150 (83.3)

[a] Parameter estimate (%RSE).

ACR=American College of Rheumatology; AUC_{0-24w}=cumulative area under the concentration-time curve from Week 0 to Week 24 (unit: day*µg/mL); $\beta_0/\beta_1/\beta_2$=baseline response rate in logit scale where $\beta_0=\beta_1-d_0$ and $\beta_2=\beta_1+d_2$; BDAS=baseline Disease Activity Score in 28 joints; BPAS=baseline Psoriasis Area and Severity Index score; $C_{ave,ss}$=average concentration at steady state (unit: µg/mL); $C_{trough,wk20}$=trough serum concentration at Week 20 (unit: µg/mL); EC_{50}=guselkumab exposure at half maximum drug effect (unit: same as the respective pharmacokinetic metrics in the exposure-response analysis); E_{max}=maximum drug effect in logit scale; RSE=relative standard error

Final performance of the models of ACR responses were assessed via the goodness-of-fit plots displayed in Figures 5.4.3.5-7. Overall, these models provide an adequate fit to the observed E-R data. The wider 90% CIs of the predicted ACR responses in the lower exposure quartiles are consistent with the relatively higher %RSE of EC50, which indicates a lack of efficacy data in the lower exposure range.

Figure 5.3.4.5: Goodness-of-fit Plot of ACR20/50/70 at Week 24 Using AUC0-24w as Exposure Metric

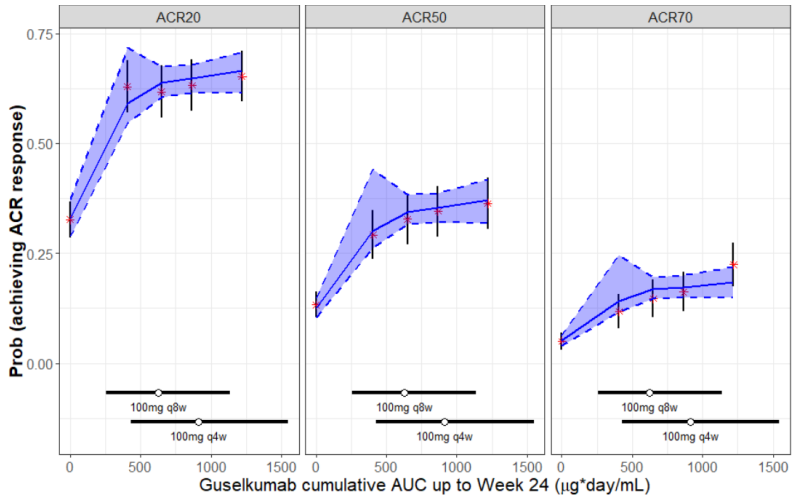


Figure 5.3.4.6: Goodness-of-fit Plot of ACR20/50/70 at Week 24 Using Cave,ss as Exposure Metric

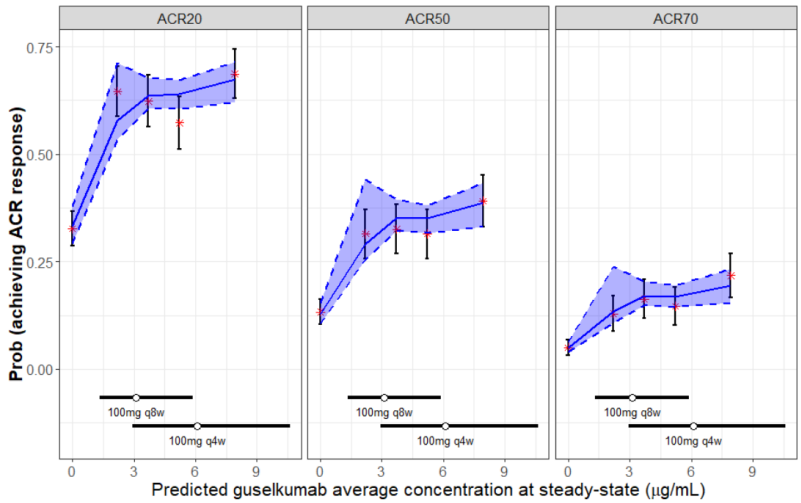
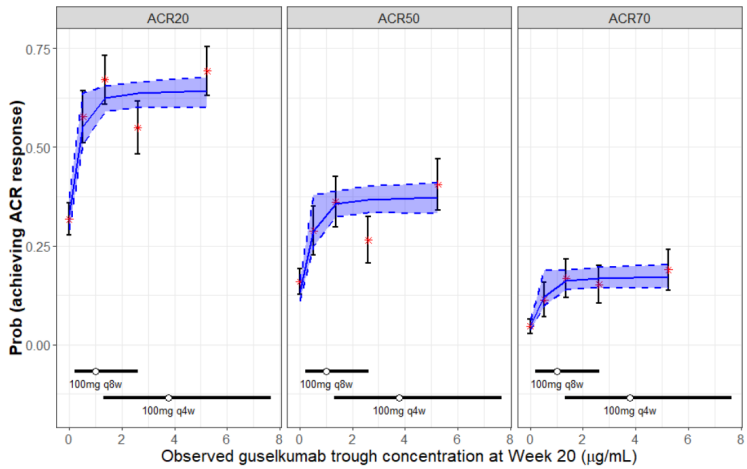


Figure 5.3.4.7: Goodness-of-fit Plot of ACR20/50/70 at Week 20 using Ctrough,wk20 as Exposure Metric



In Figures 5.3.4.5-7 the observed ACR20/50/70 response rates (red asterisk) and corresponding 90% confidence intervals were determined according to the bins for the model-predicted guselkumab exposure metrics and were plotted as the median exposure for each bin. The solid blue lines are the simulated median responses. The dotted blue lines and shaded areas both represent the simulated 90% prediction intervals from 1,000 simulations incorporating model parameter uncertainties. The solid black lines at the

bottom of the chart show the 5th to the 95th percentile for the exposure metrics, and the open circles are plotted at the median values for the 100 mg q8w and 100 mg q4w treatment groups, respectively.

For the 2 E-R models for IGA 0/1 and IGA 0 responses, the baseline PASI score was identified as a covariate on the intercept and E_{max} for both models, with a trend showing that subjects with lower baseline PASI score had higher IGA 0/1 and IGA 0 responses. No other covariate was identified as having a significant effect on the analyses. The parameter estimates of the final E-R models for IGA 0/1 and IGA 0 responses are summarized in Table 5.3.4.2. Model parameters in the final IGA models were, in general, reasonably estimated. Overall, the modeling results for IGA 0/1 and IGA 0 at Week 24, including the covariates effects identified, were consistent between the 2 exposure metrics (ie, model-predicted $AUC_{0\text{-}24w}$ or $C_{ave,ss}$), indicating robustness of the IGA E-R models.

Table 5.3.4.2 Parameter Estimates of the Final Exposure-response Model for IGA 0/1 and IGA 0 Response at Week 24

Parameters	**Week 24 using $AUC_{0\text{-}24w}$[a]**	**Week 24 using $C_{ave,ss}$[a]**
IGA Categorical Modeling		
Run#	402	502
β_1	-0.450 (27.6)	-0.447 (27.8)
BPAS on β_1	-0.779 (16.6)	-0.785 (16.4)
d_0	1.91 (5.45)	1.93 (5.51)
E_{max}	3.05 (10.9)	3.09 (9.27)
BPAS on E_{max}	0.217 (27.9)	0.214 (27.8)
EC_{50}	166 (48.3)	0.922 (39.5)

[a] Parameter estimate (%RSE).

$AUC_{0\text{-}24w}$=cumulative area under the concentration-time curve from Week 0 to Week 24 (unit: day*µg/mL); β_0/β_1=baseline response rate in logit scale where $\beta_0=\beta_1-d_0$; BPAS=baseline Psoriasis Area and Severity Index score; $C_{ave,ss}$=average concentration at steady state (unit: µg/mL); EC_{50}=guselkumab exposure metrics to reach 50% maximum drug effect (unit: same as the respective pharmacokinetic metrics in the exposure-response analysis); E_{max}=maximum drug effect in logit scale; IGA=Investigator's Global Assessment; IGA 0=IGA score of cleared (0); IGA 0/1=IGA score of cleared (0) or minimal (1); RSE=relative standard error

The performances of the final models of IGA responses at Week 24 were assessed via goodness-of-fit plots, which are displayed in Figure 5.3.4.8-9.

Figure 5.3.4.8: Goodness-of-fit Plot of IGA0/1 and IGA0 at Week 24 Using AUC0-24w as the Exposure Metric

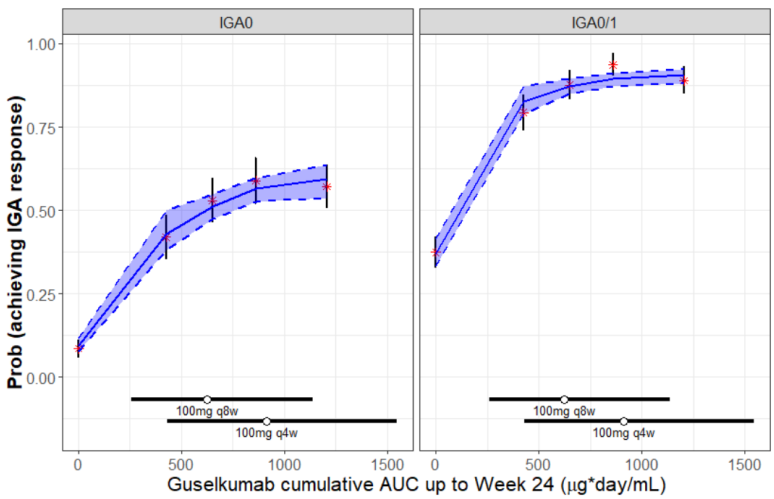
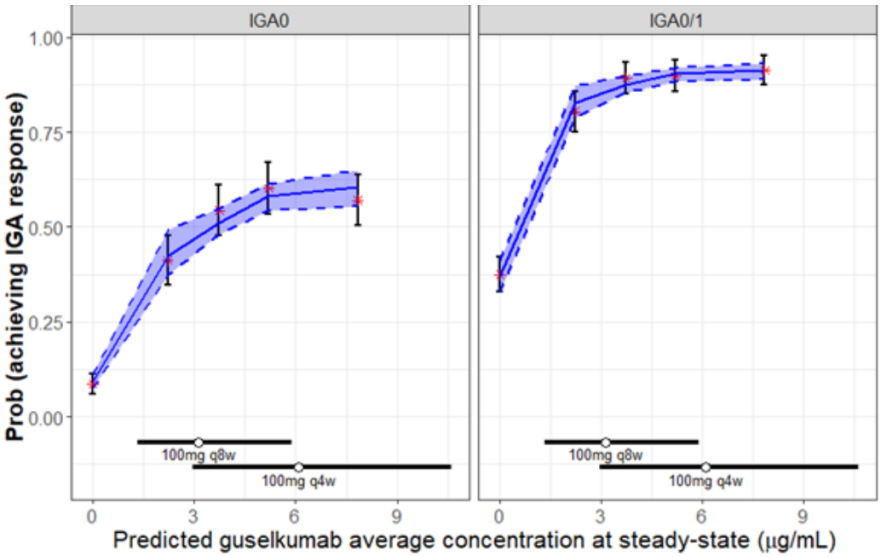


Figure 5.3.4.9: Goodness-of-fit Plot of IGA0/1 and IGA0 at Week 24 Using Cave,ss as Exposure Metric



In figures 5.3.4.8-9, the observed IGA0/1 and IGA0 response rates (red asterisks) and corresponding 90% confidence intervals were determined according to the bins of the model-predicted guselkumab exposure metrics, and were plotted as median exposure for each bin. The solid blue lines are the simulated median responses. The dotted blue lines and shaded areas both represent the simulated 90% prediction intervals from 1000 simulations incorporating model parameter uncertainties. The solid black lines at the bottom of the chart show the 5th to the 95th percentile for the exposure metrics, and the open circles are plotted at the median values for the 100 mg q8w and 100 mg q4w treatment groups, respectively.

Simulations

To quantify ACR20/50/70, IGA0/1, and IGA0 responses following the dose regimens studied in the Phase 3 studies, 100 mg q8w and 100 mg q4w, and in subpopulations stratified by the covariates identified in the E-R analyses, final E-R models were used to simulate ACR and IGA responses taking into account the model parameter uncertainties.

The model-predicted ACR20/50/70 responses at Week 24 and Week 20 grouped by baseline DAS28 score (≤5.1 versus >5.1) or by baseline PASI score (≤5.8 versus >5.8) for 100 mg q8w and 100 mg q4w, are presented in Tables 5.3.4.3-5.3.4.4.

Table 5.3.4.3: Summary of Simulated ACR20/50/70 Outcomes: ACR Responses ~ AUC0-24w

	ACR	Model-predicted Response Rate (90% CI)[a]			Median Difference (q4w vs q8w)
		Placebo	100 mg q8w	100 mg q4w	
Overall	ACR20	0.330 (0.289, 0.373)	0.628 (0.593, 0.685)	0.648 (0.614, 0.680)	0.020
	ACR50	0.125 (0.105, 0.150)	0.335 (0.308, 0.399)	0.354 (0.321, 0.389)	0.019
	ACR70	0.051 (0.041, 0.064)	0.162 (0.141, 0.209)	0.175 (0.150, 0.202)	0.013
Stratified by Baseline DAS28 (BDAS)					
BDAS ≤5.1	ACR20	0.330 (0.289, 0.373)	0.667 (0.630, 0.716)	0.686 (0.645, 0.722)	0.019
	ACR50	0.125 (0.105, 0.150)	0.374 (0.340, 0.435)	0.394 (0.352, 0.438)	0.020
	ACR70	0.051 (0.041, 0.064)	0.187 (0.160, 0.238)	0.199 (0.169, 0.233)	0.012
BDAS >5.1	ACR20	0.330 (0.289, 0.373)	0.584 (0.547, 0.647)	0.601 (0.564, 0.635)	0.017
	ACR50	0.125 (0.105, 0.150)	0.292 (0.262, 0.365)	0.305 (0.273, 0.342)	0.013
	ACR70	0.051 (0.041, 0.064)	0.135 (0.115, 0.186)	0.142 (0.122, 0.171)	0.007
Median Diff. (BDAS ≤5.1 vs >5.1)	ACR20	0	0.083	0.085	
	ACR50	0	0.082	0.089	
	ACR70	0	0.052	0.057	

[a] Model-predicted median response rates with 90% CIs.

Abbreviations: ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; $AUC_{0\text{-}24w}$=cumulative area under the concentration-time curve from Week 0 to Week 24; BDAS=baseline DAS28 score; CI=confidence interval; DAS28=Disease Activity Score in 28 joints; q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Table 5.3.4.4: Summary of Simulated ACR20/50/70 Outcomes: Responses ~ Ctrough,wk20

	ACR	Model-predicted Response Rate (90% CI)[a]			Median Difference (q4w vs q8w)
		Placebo	100 mg q8w	100 mg q4w	
Overall	ACR20	0.329 (0.289, 0.371)	0.590 (0.556, 0.636)	0.642 (0.604, 0.673)	0.052
	ACR50	0.134 (0.112, 0.161)	0.324 (0.293, 0.371)	0.372 (0.336, 0.408)	0.048
	ACR70	0.050 (0.039, 0.062)	0.144 (0.122, 0.178)	0.172 (0.145, 0.201)	0.028
Stratified by Baseline DAS28 (BDAS)					
BDAS ≤5.1	ACR20	0.329 (0.289, 0.371)	0.628 (0.592, 0.672)	0.679 (0.641, 0.714)	0.051
	ACR50	0.134 (0.112, 0.161)	0.361 (0.325, 0.409)	0.413 (0.371, 0.455)	0.052
	ACR70	0.050 (0.039, 0.062)	0.166 (0.140, 0.200)	0.199 (0.165, 0.236)	0.033
BDAS >5.1	ACR20	0.329 (0.289, 0.371)	0.546 (0.509, 0.597)	0.589 (0.548, 0.626)	0.043
	ACR50	0.134 (0.112, 0.161)	0.281 (0.249, 0.331)	0.316 (0.280, 0.354)	0.035
	ACR70	0.050 (0.039, 0.062)	0.118 (0.099, 0.151)	0.136 (0.113, 0.161)	0.018
Median Diff. (BDAS ≤5.1 vs >5.1)	ACR20	0	0.082	0.090	
	ACR50	0	0.080	0.097	
	ACR70	0	0.048	0.063	
Stratified by Baseline PASI (BPAS)					
BPAS ≤5.8	ACR20	0.329 (0.289, 0.371)	0.552 (0.514, 0.598)	0.590 (0.547, 0.628)	0.038
	ACR50	0.134 (0.112, 0.161)	0.288 (0.257, 0.333)	0.321 (0.283, 0.359)	0.033
	ACR70	0.050 (0.039, 0.062)	0.123 (0.103, 0.151)	0.139 (0.115, 0.166)	0.016
BPAS >5.8	ACR20	0.329 (0.289, 0.371)	0.628 (0.587, 0.682)	0.678 (0.634, 0.714)	0.050
	ACR50	0.134 (0.112, 0.161)	0.359 (0.321, 0.419)	0.407 (0.365, 0.451)	0.048
	ACR70	0.050 (0.039, 0.062)	0.164 (0.137, 0.209)	0.194 (0.161, 0.231)	0.030
Median Diff. (BPAS ≤5.8 vs >5.8)	ACR20	0	-0.076	-0.088	
	ACR50	0	-0.071	-0.086	
	ACR70	0	-0.041	-0.055	

[a] Model-predicted median response rates with 90% CIs.

Abbreviations: ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; BDAS=baseline DAS28 score; BPAS=baseline Psoriasis Area and Severity Index (PASI) score; CI=confidence interval; $C_{trough,wk20}$=trough serum concentration at Week 20; q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Table 5.3.4.5 shows a summary of the predicted IGA0/1 and IGA0 responses by covariates and guselkumab dose regimens.

Table 5.3.4.5: Summary of Simulated IGA0/1 and IGA0 Outcomes: Week 24 IGA Responses ~ AUC0-24w (Run402) / ~ $Cave_{ss}$

Baseline PASI	IGA	Model-Predicted Response Rate (90% CI) [a]			Median Difference (q4w vs q8w)
		Placebo	100 mg q8w	100 mg q4w	
Week 24 IGA Responses ~ AUC_{0-24w} (Run402)					
Overall	IGA0	0.095 (0.077, 0.117)	0.503 (0.469, 0.542)	0.547 (0.507, 0.578)	0.044
	IGA0/1	0.371 (0.332, 0.416)	0.865 (0.840, 0.888)	0.885 (0.863, 0.902)	0.02
Stratified by Baseline PASI (BPAS)					
BPAS ≤5.8	IGA0	0.165 (0.128, 0.21)	0.581 (0.537, 0.626)	0.621 (0.572, 0.667)	0.040
	IGA0/1	0.548 (0.482, 0.606)	0.900 (0.879, 0.918)	0.915 (0.895, 0.931)	0.015
BPAS >5.8	IGA0	0.055 (0.042, 0.072)	0.459 (0.419, 0.507)	0.511 (0.466, 0.548)	0.052
	IGA0/1	0.272 (0.231, 0.324)	0.845 (0.814, 0.875)	0.871 (0.846, 0.892)	0.026
Median Diff. (BPAS ≤5.8 vs >5.8)	IGA0	0.110	0.122	0.110	
	IGA0/1	0.276	0.055	0.044	
Week 24 IGA Responses ~ $C_{ave,ss}$ (Run502)					
Overall	IGA0	0.092 (0.074, 0.113)	0.490 (0.456, 0.534)	0.566 (0.528, 0.602)	0.076
	IGA0/1	0.370 (0.330, 0.412)	0.860 (0.836, 0.888)	0.897 (0.876, 0.915)	0.037
Stratified by Baseline PASI (BPAS)					
BPAS ≤5.8	IGA0	0.161 (0.123, 0.204)	0.575 (0.531, 0.621)	0.637 (0.588, 0.686)	0.062
	IGA0/1	0.544 (0.486, 0.604)	0.899 (0.879, 0.92)	0.923 (0.904, 0.94)	0.024
BPAS >5.8	IGA0	0.053 (0.041, 0.069)	0.442 (0.404, 0.496)	0.533 (0.49, 0.577)	0.091
	IGA0/1	0.271 (0.226, 0.319)	0.839 (0.807, 0.873)	0.885 (0.86, 0.906)	0.046
Median Diff. (BPAS ≤5.8 vs >5.8)	IGA0	0.108	0.133	0.104	
	IGA0/1	0.273	0.060	0.038	

[a] Model-predicted median response rates and 90% CIs.

Abbreviations: AUC_{0-24w}=cumulative area under the concentration-time curve from Week 0 to Week 24; BPAS=baseline Psoriasis Area and Severity Index (PASI) score; $C_{ave,ss}$=average concentration at steady state; CI=confidence interval; IGA=Investigator's Global Assessment; IGA0=IGA score of cleared (0); IGA0/1=IGA score of cleared (0) or minimal (1); q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Exposure-response Analysis for Safety

The proportions of subjects who had AEs, SAEs, AEs leading to discontinuation of study agent, infections and serious infections through Week 24 were evaluated with respect to observed steady-state trough serum guselkumab concentration quartiles for each dose group using pooled data from PSA3001 and PSA3002. The steady-state trough serum guselkumab concentrations at Week 20/24 were divided into 4 groups with approximately equal numbers of subjects in each group based on quartiles for each dose group.

For both dose groups, no apparent relationships were observed between the incidence of AEs, SAEs, AEs leading to discontinuation of study agent, infections and serious infections through Week 24 and quartiles of trough steady-state serum guselkumab concentrations at Week 20 (100 mg q8w) or Week 24 (100 mg q4w). In addition, no apparent differences in the incidence of these safety parameters of interest between the 2 dose groups were observed.

Table 5.3.4.6: Summary of Overall Treatment-Emergent Adverse Events Through Week 24 by Quartile of Trough Serum Guselkumab Concentration at Steady-state; Pharmacokinetic Analysis Set (Studies PSA3001 and PSA3002)

	Guselkumab									
	100 mg W0, 4+q8w (Week 20)[a]					100 mg q4w (Week 24)[b]				
	< 1st Quartile	≥ 1st Quartile to < 2nd Quartile	≥ 2nd Quartile to < 3rd Quartile	≥ 3rd Quartile	Combined	< 1st Quartile	≥ 1st Quartile to < 2nd Quartile	≥ 2nd Quartile to < 3rd Quartile	≥ 3rd Quartile	Combined
Analysis set: Pharmacokinetic Analysis Set	81	82	82	82	327	67	67	67	68	269
Average duration of follow up (weeks)	24.0	24.0	24.0	24.0	24.0	24.0	23.9	24.0	24.0	24.0
Average exposure (number of guselkumab administrations)	4.0	4.0	4.0	4.0	4.0	6.0	6.0	6.0	6.0	6.0
Subjects with 1 or more adverse events	41 (50.6%)	39 (47.6%)	35 (42.7%)	34 (41.5%)	149 (45.6%)	24 (35.8%)	32 (47.8%)	30 (44.8%)	30 (44.1%)	116 (43.1%)
Subjects with 1 or more serious adverse events	2 (2.5%)	2 (2.4%)	0	1 (1.2%)	5 (1.5%)	0	0	0	1 (1.5%)	1 (0.4%)
Subjects with 1 or more adverse events leading to discontinuation of study agent	1 (1.2%)	0	0	0	1 (0.3%)	0	0	0	0	0
Subjects with 1 or more infections	15 (18.5%)	16 (19.5%)	14 (17.1%)	13 (15.9%)	58 (17.7%)	12 (17.9%)	12 (17.9%)	6 (9.0%)	8 (11.8%)	38 (14.1%)
Subjects with 1 or more serious infections	0	1 (1.2%)	0	0	1 (0.3%)	0	0	0	0	0

[a] Trough serum guselkumab concentration for 100 mg q8w at Week 20: Q1=0.53 µg/mL, Q2=1.01 µg/mL, Q3=1.6 µg/mL.
[b] Trough serum guselkumab concentration for 100 mg q4w at Week 24: Q1=2.72 µg/mL, Q2=4.08 µg/mL, Q3=5.67 µg/mL.
q4w=every 4 weeks; q8w=every 8 weeks

[TPKSF01.RTF] [CNTO1959\Z_SCP\DBR_2019_04\RF_PSA_SBLA\PROD\TPKSF01.SAS] 21MAY2019, 21:35

Overall, the incidence of these safety parameters of interest were not associated with steady-state trough serum guselkumab concentrations.

To further explore the relationships between guselkumab PK exposure and safety, incidence of safety parameters of interest (ie, AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections) through Week 24 were evaluated with respect to model-predicted exposure parameters (ie, C_{max}, $Cave_{,ss}$, and AUC_{0-24w}) by dose group using the pooled data from the Phase 3 studies (PSA3001 and PSA3002). All PK exposure parameters were derived from the final population PK model using individual post hoc PK parameter estimates and the actual administration information for each individual subject.

For both dose groups, no apparent relationships were observed between the incidence of AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections through Week 24 and

quartiles of C_{max}AUC$_{0-24w}$ In addition, no apparent differences in the incidence of these safety parameters of interest between the 2 dose groups were observed.

2.3.5. Discussion on clinical pharmacology

Guselkumab displays PK properties typical of a human IgG1-type immunoglobulin interacting with a soluble target, i.e. a low clearance and a low total volume of distribution. Therefore, it was not expected that guselkumab kinetics in PsA patients would be different from PsO patients. Indeed across the Phase 3 PsA studies (ie, the pooled data set), the median steady state trough serum guselkumab concentrations were 1.01 µg/mL (mean±SD: 1.18±0.87 µg/mL) in the 100 mg q8w group and 3.50 µg/mL (mean±SD: 3.83±1.92 µg/mL) in the 100 mg q4w group. These values are very close to the trough concentration values reported in the PsO Phase III studies. Similarly, in both patient groups trough serum guselkumab concentrations reached steady state by Week 20 for the 100 mg q8w group and by Week 12 for the 100 mg q4w group. Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and csDMARDs such as methotrexate, did not affect the clearance of guselkumab.

Not only the observed concentrations but also the POP-PK parameter estimates are essentially the same. The methods used for the development and evaluation of the population PK model were appropriate and the model diagnostics indicated that the model describes the data adequately. All parameters were estimated with good precision (RSE<17%). The eta-shrinkages for CL/F and V/F was relatively low (<15%). The eta-shrinkage for Ka was relatively large. This is not pursued since maintaining adequate exposure levels (eg. trough or AUC) is mainly driven by CL/F. The VPCs show that the predictive ability of the model is adequate.

The typical population estimates for apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.596 L/day and 15.5 L, respectively, with a median body weight of 84 kg. The model-derived elimination half-life was approximately 18.1 days. The corresponding values in PsO patients were 0.516 L/day, 13.5 L and 18.1 days which again demonstrates close similarity.

Body weight and diabetic comorbidity were identified as significant covariates on guselkumab PK. Exposures (trough and AUC) were around 30% lower in PsA subjects with a body weight ≥90 kg than in subjects <90 kg. Exposures in subjects with diabetic comorbidity were around 20-30% lower than in subjects without diabetic comorbidity.

In this analysis, body weights of subjects ranged from 46.0 to 203 kg. The MAH showed that despite differences in PK exposure in different body weight subgroups, the efficacy and safety were generally comparable between the two dose regimens. Also, in subjects with diabetic comorbidity and body weight >100 kg, simulated exposure metrics were lower versus subjects without diabetic comorbidity and body weight <100 kg. However, subgroup analyses showed comparable efficacy between the 2 dose regimens in subjects with diabetic comorbidity and high body weight (>100 kg). Therefore, the CHMP agreed that body weight-based dose adjustment is not needed.

No specific studies have been conducted in elderly patients. Of the 1384 plaque psoriasis patients exposed to guselkumab in phase III clinical studies and included in the population pharmacokinetic analysis, 70 patients were 65 years of age or older, including 4 patients who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. Accordingly 4.2 of the SmPC outlines that there is limited information in subjects aged ≥ 65 years and very limited information in subjects aged ≥ 75 years.

Population pharmacokinetic analyses in plaque psoriasis and psoriatic arthritis patients indicated no apparent changes in CL/F estimate in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Prior exposure to anti-TNFα agents did not have an apparent impact on the incidence of antibodies to guselkumab and the overall incidence of antibodies to guselkumab through Week 24 was low in subjects with PsA (2.0%, 15 of 744 subjects). This value is comparable to PsO patients (5.4%) considering later value represent a pooled estimate from the Phase 2 dose-ranging study (PSO2001 through Week 40) and 2 Phase 3 studies (PSO3001 through Week 44 and PSO3002 through Week 48). The longer duration justifies the higher antibody incidence rates. Concomitant use of methotrexate (MTX), non-biologic disease-modifying antirheumatic drugs (DMARDs), corticosteroids, or nonsteroidal anti-inflammatory drugs did not have an apparent impact on the CL/F of guselkumab. However, the incidence of antibodies to guselkumab appeared to be lower in subjects with concomitant use of MTX (1.4%) or non-biologic DMARDs (1.6%) compared to subjects without concomitant use of MTX (2.8%) or non-biologic DMARDs (2.9%). The SmPC currently reports the 24 weeks immunogenicity results of the two-Phase III studies. It was agreed that SmPC should be updated with the final immunogenicity results when both studies are finalized. The final study report for PSA3001 is planned to be submitted by December 2021 as outlined in the RMP.

While from a PK perspective there is no difference between PsA and PsO patients, the two patient populations can be different regarding the needed skill to self-administer the product. In the Type II variation II/0002/G the MAH introduced a new delivery device called SelfDoseTM while in the three PsA trials an injection device called UltraSafe PLUS™ was used. The CHMP accepted then that there is no difference between the two devices in PsO patients, including the potential for self-administration. The MAH also clarified that a Summative Human Factors Study (HFS) already has been conducted with the SelfDose (PFS-S) device in PsA patients. This study included hand impaired patients and psoriatic patients. In this study all participants (45/45, 100%) stated that they had no difficulty using the SelfDoseTM device. Therefore, the CHMP agreed that the use of the PFS-S device in the clinical studies supporting the PsA indication was not required.

The pattern of changes in the biomarker levels is consistent with the presumed mode of action of guselkumab. In the combined biomarker study population subset, a strong pharmacodynamic effect was observed with both 100mg q4w and 100mg q8w dosing regimens of guselkumab. Guselkumab resulted in decreases in serum CRP, SAA, IL-6, IL-17A, IL-17F, and IL-22 as early as Week 4, while no significant change was observed in the placebo arms at Week 4. Expression of these proteins continued to decrease further by Week 24 ($p<0.05$ and geometric mean decrease from baseline ≥ 33%) in guselkumab treated subjects on either dosing regimen. These results are reflected in 5.1 of the SmPC. Further, week 24, IL-17A and IL-17F expression was no longer significantly different for subjects treated with either dose of guselkumab suggesting a normalization of peripheral effector cytokines associated with the IL-23/Th17 axis following treatment with guselkumab. There was no significant treatment-specific Week 24 ACR20 or IGA response association with change from baseline in serum proteins. Therefore, the PD effect on biomarkers is unquestionable but this effect does not seem directly related to clinical PsA specific clinical response (ACR20, IGA) except that IL-17F levels were reduced to a greater extent in PASI75 responders compared to PASI75 non-responders, indicating a response specific association. No difference can be seen between the q4w and q8w regimens' PD effects. A plausible hypothesis that the PD effects in both cases are maximal, on the plateau. The mechanistic explanation of this plateau effect is missing. To better understand of this missing link, investigating the guselkumab /IL23 plasma concentration ratio following the 100 mg q8w dose regimen and the 100 mg q4w dose regimens was suggested. However, this suggestion could not be followed due to the inability of the assay to detect free IL-23 versus that which is guselkumab-bound. This issue was not further pursued by the CHMP.

Ordered logistic regression (also called the logit model or cumulative link model) was used to model the relationship between the ordered ACR20/50/70 responses and the PK metrics such as the observed Ctrough and the population PK model-predicted AUC0-24w and Cavess. Similar analysis was conducted for IGA0/1, and IGA0 responses at Week 24 using pooled data from Studies PSA3001 and PSA3002. Logistic regression models, assuming an Emax relationship between the PK exposure metrics and efficacy response rates, adequately described the observed data, as indicated by goodness-of-fit plots. ACR20/50/70 responses using different exposure metrics (AUC0-24w, Cavess, and Ctrough) the baseline DAS28 score was identified as a covariate based on Emax, with a trend indicating that subjects with lower baseline DAS28 scores had higher ACR20/50/70 responses. The DAS28 effect is quite remarkable particularly if ACR response is corrected with the placebo response. For ACR20 the corresponding values are 29.9% and 21.7% in the q8w group and 35.0% and 26% in q4w group. Thus, the placebo corrected response rates are 27% and 25% lower in the high DAS28 (>5.1) patient group compared the low DAS28 group (<5.1). The MAH conducted additional simulations which showed that the ACR20 difference between the low and high BDAS groups is about 5%-6%. These data indicate that the effect of guselkumab is additive rather than multiplicative. Therefore, at lower disease activity (lower BDAS) the effect on relative metrics such as ACR20 is higher. This seems to be a class effect shown by other anti-PSA biologicals .

The E-R models also predict that dose regimen of 100 mg q4w would result in minor increases in IGA0/1 and IGA0 responses compared to 100 mg q8w. For the overall population, the E-R models predict that the differences between the 2 dose regimens are less than 4% for IGA0/1 response and approximately 4% to 8% for IGA0 response. Similar magnitudes of differences were predicted between the 2 dose regimens for the baseline PASI subgroups: less than 5% for IGA0/1 response and approximately 4% to 9% for IGA0 response. Overall, model-predicted differences between the 100 mg q8w and 100 mg q4w dose regimens were less than 5% to achieve IGA0/1, and 4% to 9% to achieve IGA0. These results indicate that 100 mg q4w only have a small incremental benefit on achieving IGA0 response compared to 100 mg q8w. It is however acknowledged that in the overall PsA study population, the effect of q4w maintenance dose on inhibition of radiographic progression was higher (and significant) than with q8w maintenance dose (non significant) at week 24. This supports an incremental benefit of the guselkumab q4w maintenance dose regimen on inhibition of structural damage compared to the q8w regimen for patients at high risk for joint damage according to clinical judgement. It is agreed that in some patients' a deeper suppression of the disease activity is needed as well as a need to be controlled as soon as possible, which would not be sufficient with Q8W regimen. While there are potential risks associated with the q4w regimen, these can be managed by frequent liver monitoring. (See discussions on efficacy and safety).

2.3.6. Conclusions on clinical pharmacology

The MAH adequately characterized the PK of guselkumab using sample collected in 1 Phase II and 2 Phase III trials. Descriptive and POP-PK analysis did not reveal difference from the previous results in PsO patients.

2.4. Clinical efficacy

The 3 PsA studies included a target population of adult subjects diagnosed with active PsA and who met ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening (Taylor et al, 2006).

Subjects with prior exposure to anti-tumor necrosis factor alpha (TNFα) agents were allowed in

studies PSA2001 (1 anti-TNFα agent limited to 20% of the study population) and PSA3001 (up to 2 anti-TNFα agents and limited to approximately 30% of the study population).

Subjects in study PSA3002 were required to be biologic-naïve in order to enrol a population with higher disease burden and to increase the power for detection of a treatment effect for guselkumab on the radiographic endpoints.

2.4.1. Dose response study(ies)

No specific dose-response studies were performed.

Two different posologies were proposed: 1. guselkumab 100 mg at Weeks 0 and 4 then every 8 Weeks; 2. 100 mg Every 4 Weeks

Rationale for Guselkumab 100 mg at Weeks 0 and 4 then Every 8 Weeks Dose Regimen

- This dose regimen was evaluated in the Phase 2 PsA study (CNTO1959PSA2001) and in the 2 global Phase 3 studies in psoriasis. In the CNTO1959PSA2001 study, clinically meaningful improvement was observed with this dose regimen in all important domains of PsA in patients with active PsA and ≥3% BSA of psoriasis. Additionally, significant benefit was also observed with this dose regimen on plaque psoriasis in patients with moderate-to-severe psoriasis in the Phase 3 psoriasis studies.
- An additional dose was included at Week 4 to ensure that trough guselkumab levels do not fall below those obtained at steady-state levels. This additional Week 4 dose results in a slightly higher Cmax and Ctrough in the first 12 weeks than those at steady state (~21% and ~18%, respectively) and may result in a more rapid onset of response.
- The safety of this dose regimen has been established in a large psoriasis development program as well as in PsA and RA Phase 2 studies.

Rationale for Guselkumab 100 mg Every 4 Weeks Dose Regimen

- A dose regimen of 100 mg q4w was included to determine if more frequent dosing may achieve higher efficacy in PsA.
- In the overall PsA study population, the effect of q4w dose on inhibiton of radiographic progression was higher (and significant) than with q8w dose (non significant) at week 24. some patients' a deeper suppression of the disease activity is needed as well as a need to be controlled as soon as possible, which would not be sufficient with Q8W regimen.
- Modeling analyses based on data from CNTO1959PSA2001 suggested that a higher or more frequent dose regimen may achieve better efficacy in PsA.
- Literature data (Husted et al, 1998) suggested that patients who have had inadequate response to anti-TNFα or other biologic treatments may benefit from a higher dose.

However, subgroup analysis of prior TNF-alfa I use in studies PSA2001 and PSA3001 showed no impact of prior TNF alfa use on the efficacy of guselkumab. This finding also should be handled with caution, since there was only a few (much less than the prespecified limit) patients with prior TNF-alfa experience.

Guselkumab has been shown to have an acceptable safety profile in multiple patient populations, including with a higher dose regimen that was studied in a Phase 2 RA study (200 mg q8w).

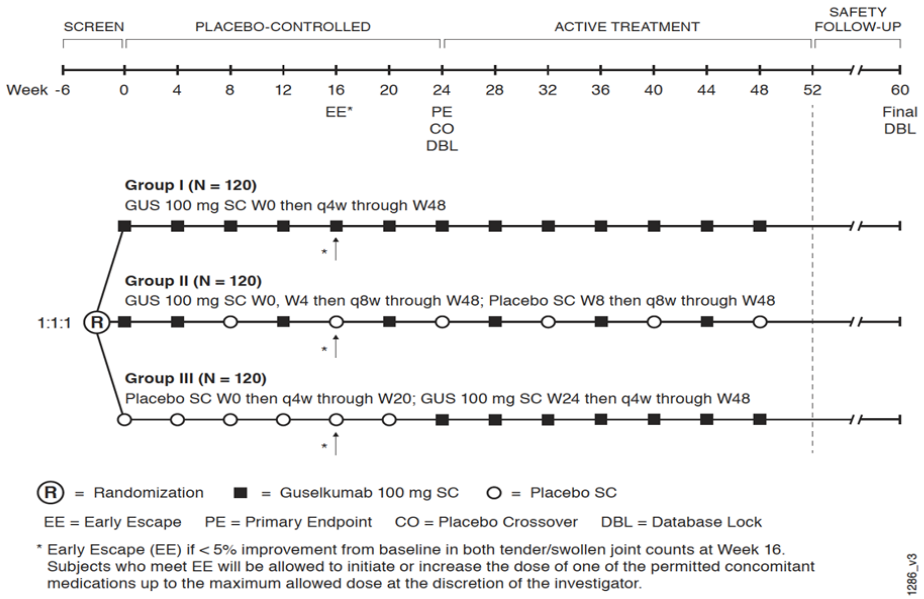
2.4.2. Main studies

Phase-3 clinical studies CNTO1959PSA3001 (DISCOVER-1) and CNTO1959PSA3002 (DISCOVER-2)

Methods

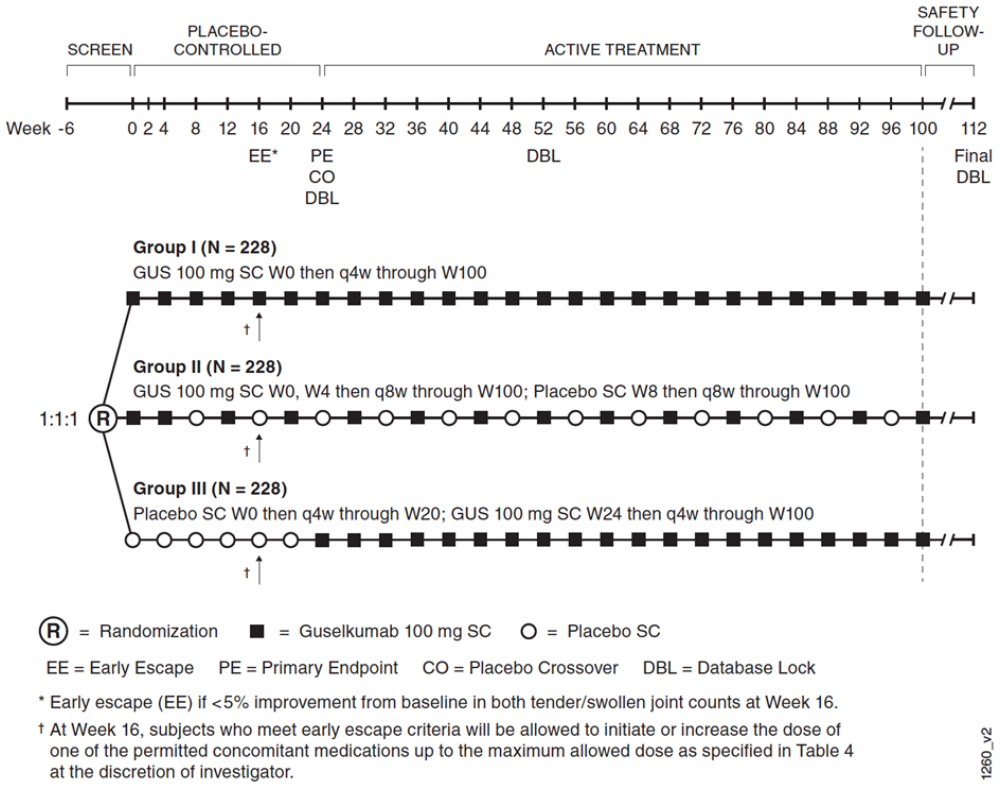
Study PSA3001 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of guselkumab in subjects with active PsA who had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, or NSAIDs).

Figure 5.4.2.1 Study Schema for the Phase 3 PsA Study CNTO1959PSA3001



Study PSA3002 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of guselkumab in subjects with active PsA who had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, or NSAIDs). Subjects were required to be biologic naïve in this study.

Figure 5.4.2.2 Study Schema for the Phase 3 PsA Study CNTO1959PSA3002



Study participants

PSA3001: The target population consisted of adult men or women with active PsA who have had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast or NSAIDs). In addition, approximately 30% of the study population may have been previously exposed to up to 2 anti-**TNFα** agents.

PSA3002: The target population consisted of adult men or women with active PsA who were biologic naïve and had an inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, and/or NSAIDs). Additionally, a biologic naïve population with a CRP ≥0.6 mg/dL was required to enrich the population for radiographic progression and increase the power for detection of treatment effect on radiographic endpoints.

Key inclusion criteria not mentioned above:

- diagnosed with PsA for at least 6 months prior to the first administration of study agent,
- meet ClASsification criteria for Psoriatic ARthritis (CASPAR Taylor et al, 2006) at screening.
- Subjects must have had active PsA as defined by ≥3 tender and ≥3 swollen joints (PSA3001) or ≥5 tender and ≥5 swollen joints (PSA3002) at both screening and baseline,
- CRP ≥0.3 mg/dL (PSA3001) or CRP ≥0.6 mg/dL (PSA3002) at screening.
- at least 1 of the PsA subsets: distal interphalangeal (DIP) joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. In addition, subjects must have had active plaque psoriasis with at least 1 psoriatic plaque of ≥2 cm in diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis.

- Subjects were permitted to continue stable doses of MTX (≤25 mg/week), low-dose oral corticosteroid (≤10 mg of prednisone per day or equivalent), or NSAIDs and other analgesics treatment during the study. If they were not using these medications at baseline, these medications must be stopped ≥4 weeks (for MTX) or ≥2 weeks (for NSAIDs and other analgesics or oral corticosteroid) prior to the first administration of study agent.

Common key exclusion criteria for PSA3001 and 3002

- subjects with other inflammatory diseases including but not limited to rheumatoid arthritis, axial spondyloarthritis, system lupus erythematosus, or Lyme disease
- subjects with the form of nonplaque or current drug-induced psoriasis
- Subjects with prior exposure to Janus kinase inhibitors, Non-biologic DMARDs other than MTX, systemic immunosuppressants, and apremilast were prohibited within 4 weeks as specified in the protocol before the first study agent administration.
- Epidural, intra-articular, intramuscular, or IV corticosteroids were prohibited within 4 weeks prior to the first administration of study agent.
- Phototherapy, systemic or psoriasis medications were also not allowed within 4 weeks, and topical psoriasis agents must have been stopped ≥2 weeks before the first study agent administration.

Additional exclusion criteria for PSA3001 only:

- subjects with prior biologic treatments other than up to 2 anti-TNFα agent for PsA or psoriasis, including but not limited to guselkumab, ustekinumab, or any other therapeutic agent targeted at IL-12, IL-17, or IL-23. Anti-TNFα agents received prior to the study entry must have been washed out before the first study agent administration.

Additional exclusion criteria for PSA3002 only:

- subjects with any prior biologic treatments

Treatments

All study agents (guselkumab and placebo) were administered through SC injection by a health care professional (HCP) at Week 0 and Week 4 and from Week 8 onwards, , subjects had the option to self-administer study agent at the investigative site.

Eligible subjects were randomly assigned to receive 1 of the following 3 treatments at Week 0:

- Guselkumab 100 mg q4w: Subjects received SC guselkumab 100 mg q4w from Week 0 through Week 48.
- Guselkumab 100 mg at Weeks 0 and 4 then q8w : Subjects received SC guselkumab 100 mg at Week0 and Week4 than q8w from Week 4 through Week 48.
- Placebo: Subjects received SC placebo q4w from Week 0 to Week 20, and crossed over at Week 24 to receive SC guselkumab 100 mg q4w from Week 24 through Week 48.

Objectives

Primary Objective

To evaluate the efficacy, safety and tolerability of guselkumab in subjects with active psoriatic arthritis (PsA)

Secondary Objectives

The secondary objectives were to evaluate the efficacy of guselkumab in improving physical function and quality of life and on psoriatic skin lesions as well as to evaluate the pharmacokinetics (PK), pharmacodynamics, safety, tolerability and immunogenicity of guselkumab in subjects with active PsA. In PSA3002 study the evaluation of the effect of guselkumab on progression of structural damage was also a secondary objective.

Outcomes/endpoints

Primary endpoint

The primary endpoint of this study is the proportion of subjects who achieve an ACR 20 response at Week 24.

Major Secondary Endpoints

Major secondary endpoints were the change from baseline in the HAQ-DI score at Week 24, ACR20 response rate at Week 16, ACR50 response rate at Week 24, percent improvement in dactylitis scores at Week 24 among subjects with dactylitis, enthesitis scores (LEI) at Week 24 among subjects with enthesitis at baseline, DAS28(CRP) -related endpoints, PASI75 response rate at Week 24 and modified van der Heijde Sharp (vdH-S) score for PSA3002 only.

Further measures of PsA disease activity included:ACR components, proportion of patients with Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA), Psoriatic Arthritis Disease Activity Score (PASDAS), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Score (GRACE), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) , Disease Activity Index for Psoriatic Arthritis (DAPSA), Routine Assessment of Patient Index Data 3 Scores (RAPID 3), Assessment of Skin Disease Activity included Physician's Global Assessment of Disease Activity, HAQ-DI, dactylitis and ethesitis assessment (resolution of dactylitis/enthesitis, dactylitis score, LEI enthesitis score), 36-item Short Form Health survey (SF-36), PASI and IGA scores, and Modified Composite Psoriatic Disease Activity Index (mCPDAI, PSA3002 only), EuroQol five dimensions questionnaire (EQ-5D)(PSA3002 only).

Pharmacokinetic and immunogenicity evaluations

Venous blood samples were collected for the determination of serum guselkumab concentrations and detection of antibodies to guselkumab or antibodies to ustekinumab.

Sample size

Study PSA3001

In order to ensure a statistical power of >90% at the significance level of 0.05 (2-sided), assuming that each of guselkumab 100 mg groups achieves an ACR 20 response of 40% compared with the placebo group response of 20% at Week 24, a total of 360 subjects were planned to be randomized in a 1:1:1 ratio to each of treatment groups.

Study PSA3002

Assuming a 45% ACR 20 response rate (primary endpoint) in the guselkumab group and a 25% ACR 20 response rate in the placebo group, a sample size of 228 subjects per treatment group (684 in total) would provide a power of approximately 99% to detect a significant treatment difference at a 2-sided significance level of 0.05.

Assuming an overall mean change of 0.9 from baseline in vdH-S score (major secondary endpoint) in the placebo group, and an overall mean change of 0.3 in the guselkumab group, and a standard deviation (SD) of 2.5 for each treatment group, a sample size of 228 subjects per treatment group (684 in total) would provide a power of approximately 90% to detect a significant treatment difference at a 2-sided significance level of 0.05.

Randomisation

Central randomization was implemented in the Phase-3 studies. At Week 0, subjects were randomly assigned (1:1:1) to 1 of 3 treatment groups (guselkumab 100 mg q4w, guselkumab 100 mg at Weeks 0 and 4 then q8w, or placebo) based on a permuted block randomization method.

Stratification factors were baseline non-biologic DMARD use (yes, no), prior exposure to anti-TNFα agents (yes, no, PSA3001 only) and the most recently available CRP value prior to randomization (<2.0 mg/dL versus ≥2.0 mg/dL; PSA3002 only).

Blinding (masking)

Blinding procedures were identical for both Phase-3 studies. Through week 24, the studies were double-blind. At week 24, the data was unblinded for analysis while subjects were still participating in the study. Identification of sponsor personnel who had access to the unblinded subject level data was documented prior to unblinding.

Statistical methods

In general, descriptive statistics, such as mean, standard deviation, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. The primary endpoint was the proportion of subjects who achieve an ACR 20 response at Week 24.

Estimands

Composite Strategy

The composite strategy assessed the treatment effect not only based on the variable measurements, but also based on intercurrent events defined as a treatment failure from the earliest date that the subject met any of the following treatment failure criteria onward through Week 24:

Discontinued study agent injections due to any reason.
Terminated study participation due to any reason.
Initiated or increased the dose of non-biologic DMARD (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA.
Initiated protocol-prohibited medications/therapies for PsA.

If a subject met any of the treatment failure criteria, the subject was considered a non-responder for response variables and had a score of no improvement (ie, no change from baseline) for continuous variables from the time the subject met any treatment failure criteria. This estimand acknowledged that meeting the treatment failure criteria was an unfavorable outcome.
The composite estimand was the main estimand analyzed for all efficacy endpoints through Week 24 except for endpoints related to joint structural damage.

Treatment policy estimand

The treatment policy strategy was to use all observed data collected for the endpoint, regardless of whether or not the subject had met any treatment failure criterion. The treatment policy estimand was analyzed as a supplementary estimand for all primary and major secondary endpoints and selected endpoints analyzed at Week 16. The treatment policy estimand was the main estimand analyzed for endpoints related to joint structural damage.

Binary Response Efficacy Endpoints

For binary response efficacy endpoints, treatment comparisons were generally performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. The magnitude of the treatment difference was estimated by the difference in response rates between the guselkumab and placebo groups with a 95% confidence interval (CI) calculated based on Wald statistics. In these analyses, subjects with missing data were imputed as not achieving the response unless otherwise specified. The Mantel Fleiss criterion was used to determine the appropriateness of using the CMH test at each visit for each treatment pair under comparison. In the event that the Mantel Fleiss criterion was not satisfied, Fisher's exact test was used instead of the CMH test to compare the two treatment groups.

Various sensitivity and supplemental analyses for the primary endpoint were performed. These evaluated the robustness of the endpoint and the impact of treatment failure criteria and missing data, and the effect of major protocol deviations that could have impacted efficacy assessment per clinical judgement.

Continuous Endpoints

For the *major secondary continuous endpoints* (HAQ-DI score, DAS28 [CRP], enthesitis score, dactylitis score, SF-36 PCS score, SF-36 MCS score, and change from baseline in modified vdH S score [PSAO3002 only]) and related continuous efficacy endpoints, treatment comparisons were performed using an analysis of covariance (ANCOVA) model based on multiple imputation (MI) data under the assumption that missing data was missing at random (MAR). The ANCOVA model included treatment group, baseline score and randomization stratification factors as the explanatory factors.

For *all other continuous efficacy endpoints*, treatment comparisons were performed using a Mixed Effect Model Repeated Measures (MMRM) model. Missing data were not imputed. For the endpoints of resolution of dactylitis and resolution of enthesitis, the analysis was stratified by the combination of study and randomization stratification factors, including treatment group. The endpoints of the change from baseline in dactylitis and change from baseline in enthesitis scores were also tested using a combination of study and randomization stratification factors as covariates in the ANCOVA model.

Hypothesis testing and Multiplicity Adjustment

The overall type I error of treatment comparison for the primary endpoint, ACR 20 at Week 24, of both guselkumab doses compared with placebo was controlled at a significance level of ≤ 0.05 using a fixed sequence procedure in the order of:

1. guselkumab 100 mg q4w group versus placebo.
2. guselkumab 100 mg q8w group versus placebo.

If the primary endpoint was significant for a guselkumab dose regimen, the overall Type I error of treatment comparison for selected major secondary endpoints was controlled at a significance level of ≤ 0.05 using a graphical multiplicity control procedure for that dose. Statistical significance was only to be claimed for multiplicity-controlled endpoints.

For all endpoints specified in the multiplicity control procedure that do not achieve statistical significance, both adjusted and nominal (unadjusted) p-values are provided. In this case, the nominal (unadjusted) p-value will be interpreted as supportive. For endpoints not included in the multiplicity control procedure, or

those that were not formally tested due to the fact that a prior endpoint did not achieve statistical significance, numerical results and nominal (unadjusted) p values are presented.

Primary Endpoint

The primary endpoint (ACR 20 response at Week 24) was analyzed at the Week 24 DBL based on the composite estimand in the full analysis set 1 (FAS1) which included all randomized subjects who received at least 1 dose (complete or partial) of study agent according to randomized treatment group, regardless of the treatment actually received. Subjects who met any treatment failure criteria prior to Week 24 were considered non-responders at Week 24, regardless of the observed ACR 20 response status. Missing data were imputed as non-responders at Week 24.The treatment difference between each guselkumab group versus the placebo group was tested using a CMH test stratified by baseline use of non-biologic DMARD (yes, no) and most recent CRP value prior to randomization (<2.0 mg/dL, ≥2.0 mg/dL). The magnitude of the treatment difference was estimated by the difference in ACR 20 response rates between the guselkumab and placebo groups with a 95% CI calculated based on Wald statistics.

Major Secondary Endpoints

All the major secondary endpoints were analyzed at the Week 24 DBL according to the randomized treatment groups. Data from all subjects in FAS1 were included with the following exceptions where endpoints were only meaningful in a subpopulation of subjects with baseline diseases:

• the analysis of the psoriasis response of IGA was based on FAS1 among the subjects with a ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

• the analysis of change from baseline in enthesitis score and resolution of enthesitis was based on FAS1 among the subjects who had at least one tender enthesis among the 6 sites included in the LEI at baseline based on data pooled from studies CNTO1959PSA3001 and CNTO1959PSA3002.

• the analysis of change from baseline in dactylitis score and resolution of dactylitis was based on FAS1 among the subjects with dactylitis at baseline based on data pooled from studies CNTO1959PSA3001 and CNTO1959PSA3002.

Sensitivity and Supplementary Analyses

To test the robustness of the primary endpoint analysis, the following sensitivity and supplementary analyses were performed.

1. To evaluate the robustness of the composite estimand regarding the assumption of all missing data as non-responder, sensitivity analyses with the exhaustive scenario tipping point analyses were performed. The analysis was conducted for an ‘exhaustive approach’ testing all combinations of missing data imputation as responder and non-responders.

2.To evaluate the impact of treatment failure and missing data handling rules, the treatment policy estimand was evaluated as a supplementary analysis. In this analysis, the observed ACR 20 response for all subjects was used regardless of whether or not treatment failure criteria were met prior to Week 24, and the missing ACR 20 response for all subjects was imputed by MI method under the assumption that data are MAR.

3. Two-dimensional tipping point analyses based on MI imputed data were included for the treatment policy estimand to assess the robustness for treatment policy estimand regarding the assumption that data are MAR.

4. The alternative composite estimand was also evaluated as a supplemental analysis. The alternative composite strategy is similar to the composite strategy however, discontinuation of study agent due to reasons other than lack of efficacy (including adverse events caused by worsening of PsA) were not

considered treatment failures. Subjects with missing data were considered non-responders. The same analysis method that was used for the primary analysis was applied.

5. A supplemental analysis based on the per-protocol strategy estimand was also performed. In this analysis, ACR response status was determined based on the last assessment up to Week 24 while subjects were on randomized treatment or the last non-missing assessment prior to meeting treatment failure criteria. This analysis used the per-protocol analysis set which included all subjects in FAS1 who met all inclusion and exclusion criteria and had no major protocol deviations that could have impacted efficacy assessment per clinical judgement.

Subgroup Analyses

Subgroup analyses were performed using a logistic regression model to evaluate treatment consistency in proportion of subjects who achieved an ACR 20 response at Week 24 over baseline demographics, baseline disease characteristics, and prior and baseline medication use. A forest plot was produced for all subgroups listed in Section 2.4 of the SAP. Odds ratios and the corresponding 95% CIs were also provided for each of the subgroups. In addition, the p-values for interaction of the treatment groups and the subgroups were provided when a subgroup had at least 2 categories.

Missing values

For all efficacy endpoints through Week 24, except for endpoints related to structural damage, subjects who met any treatment failure criteria prior to a visit were considered nonresponders (composite estimand) from that point forward. For the endpoints related to progression of structural damage in study PSA3002, all observed data collected for an endpoint were used regardless of treatment failure status (treatment policy strategy). The treatment policy estimand was used for radiographic endpoints because radiographic progression is generally a slow process and treatment discontinuation or changes in baseline medications are not anticipated to have an impact on this endpoint within the 24-week study period. The treatment policy estimand was also used for all non-radiographic major secondary endpoints as supplementary analyses to evaluate the robustness of the results with respect to the handling of treatment failure.

Subjects with missing data at Week 24 were imputed as non-responders. Sensitivity and supplementary analyses of the primary endpoint were performed to examine the robustness of the primary analysis results. Subgroup analyses were performed to evaluate consistency of treatment effect in ACR 20 response at Week 24 over baseline demographics, baseline disease characteristics, and prior and baseline medication use. All of the major secondary and other secondary binary endpoints were analyzed similarly to the primary endpoint based on the composite estimand. All endpoints were descriptively summarized by treatment groups. Treatment comparisons were performed by visit through Week 24. Nominal p-values and 95% CIs for the difference between each guselkumab group and placebo group were provided. For secondary continuous endpoints of change from baseline in HAQ-DI, DAS28 (CRP), dactylitis, enthesitis, SF-36 PCS, and SF-36 MCS, treatment comparisons were performed using an ANCOVA model based on multiple imputation (MI) data. The MI method was applied to impute the missing value(s) under the assumption of missing at random (MAR). For all other continuous efficacy endpoints, treatment comparisons were performed using a Mixed-Effect Model Repeated Measures (MMRM) model.

Pooled efficacy data

The appropriateness of pooling data from the 2 Phase 3 studies PSA3001 and PSA3002, was thought to be supported by their similar study populations , similar study designs including the same dosing regimens, the same length of placebo-controlled DB period and the same EE timing and criteria, and contemporaneous conduct.

There were two differences in the inclusion/excusion criteria: 1. CRP and joint count requirements were higher in PSA3002 than in PSA3001; 2. PSA3002 enrolled Biological DMARD-naive subjects only, whereas in PSA3001, TNF-alfa inhibitor-experienced patients were also included in a prespecified proportion.

Post-hoc analysis

Results for the analysis of the change from baseline in modified vdH-S score at Week 24 in study PSA3002 led to a series of additional analyses to determine which clinical disease characteristics are predictive variables that may identify subjects at risk of structural damage progression who might differentially benefit from the guselkumab 100 mg q4w dose regimen. Classification and regression tree (CART) analyses applied to historical placebo data were used to evaluate clinical disease characteristics in subjects with PsA to identify a subpopulation of subjects who are at high risk of structural damage progression. The analyses were performed using clinical data from placebo-treated subjects from previous clinical studies conducted by the Applicant in subjects with active PsA. The following clinical studies were included: C0168T50 (REMICADE®), C0524T08 (SIMPONI®), CNTO148PSA3001 (SIMPONI ARIA®,), CNTO1275PSA3001 (STELARA®), and CNTO1275PSA3002 (STELARA®). A total of 746 subjects who received placebo were included in this analysis. The dependent variable was based on the change from baseline in the modified vdH-S score (>0 or ≤0) at Week 24. An initial set of eight predictive variables were used: baseline values for CRP, dactylitis count, enthesitis (yes/no), PsA subtype, PsA duration, number of joints with erosion, number of joints with joint space narrowing, and number of swollen joints (based on 28 joints). These variables were chosen based on literature which suggests that subjects with worse disease characteristics are more likely to have greater radiographic progression.

Two CART analyses were completed, the first with the inclusion of baseline radiographic factors and a second without those factors. Specifically, the first analysis included radiographic data (ie, number of joints with erosion and number of joints with JSN) at baseline as predictive variables and the second was completed without these two variables. These analyses were done to reflect that in practice, radiographic information is not always available at baseline for all patients. The RPART package in R was to be used to conduct the CART analyses.

Results

Participant flow

PSA3001

Table 5.4.2.1. Summary of Study Participation Status as of Week 24; Full Analysis Set 1 (Study CNTO1959PSA3001)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	126	127	128	255	381
Subjects who did not discontinue study participation	117 (92.9%)	124 (97.6%)	125 (97.7%)	249 (97.6%)	366 (96.1%)
Subjects continuing study intervention	114 (90.5%)	123 (96.9%)	125 (97.7%)	248 (97.3%)	362 (95.0%)
Subjects who discontinued study intervention and were being followed	3 (2.4%)	1 (0.8%)	0	1 (0.4%)	4 (1.0%)
Subjects who discontinued study participation	9 (7.1%)	3 (2.4%)	3 (2.3%)	6 (2.4%)	15 (3.9%)
Subjects who completed protocol-required follow-up	2 (1.6%)	1 (0.8%)	2 (1.6%)	3 (1.2%)	5 (1.3%)
Subjects who did not complete protocol-required follow-up	7 (5.6%)	2 (1.6%)	1 (0.8%)	3 (1.2%)	10 (2.6%)
Withdrawal by subject	5 (4.0%)	1 (0.8%)	1 (0.8%)	2 (0.8%)	7 (1.8%)
Lost to follow-up	1 (0.8%)	1 (0.8%)	0	1 (0.4%)	2 (0.5%)
Death	1 (0.8%)	0	0	0	1 (0.3%)
Other	0	0	0	0	0

Early Escape at Week 16

At Week 16, 3 (2.3%) subjects in the guselkumab 100 mg q4w group, 4 (3.1%) subjects in the guselkumab 100 mg q8w group, and 24 (19.0%) subjects in the placebo group met EE criteria and were eligible for concomitant medication adjustments

Treatment failure Through Week 24

Through Week 24, 3 (2.3%) subjects in the guselkumab 100 mg q4w group, 7 (5.5%) subjects in the guselkumab 100 mg q8w group, and 21 (16.7%) subjects in the placebo group met the treatment failure criteria. The most common reasons for meeting treatment failure criteria were discontinued study agent injections due to any reason(s) (19 [5.0%] subjects) followed by initiation or increase in dose of non-biologic DMARD or oral corticosteroids over baseline for PsA (14 [3.7%] subjects).

PSA3002

Table 5.4.2.2 Summary of Study Participation Status as of Week 24; Full Analysis Set 1 (Study CNTO1959PSA3002)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	246	248	245	493	739
Subjects who did not discontinue study participation	244 (99.2%)	242 (97.6%)	238 (97.1%)	480 (97.4%)	724 (98.0%)
Subjects continuing study intervention	240 (97.6%)	240 (96.8%)	236 (96.3%)	476 (96.6%)	716 (96.9%)
Subjects who discontinued study intervention and were being followed	4 (1.6%)	2 (0.8%)	2 (0.8%)	4 (0.8%)	8 (1.1%)
Subjects who discontinued study participation	2 (0.8%)	6 (2.4%)	7 (2.9%)	13 (2.6%)	15 (2.0%)
Subjects who completed protocol-required follow-up	2 (0.8%)	4 (1.6%)	3 (1.2%)	7 (1.4%)	9 (1.2%)
Subjects who did not complete protocol-required follow-up	0	2 (0.8%)	4 (1.6%)	6 (1.2%)	6 (0.8%)
Withdrawal by subject	0	1 (0.4%)	2 (0.8%)	3 (0.6%)	3 (0.4%)
Lost to follow-up	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Death	0	0	0	0	0
Other	0	0	2 (0.8%)	2 (0.4%)	2 (0.3%)

Early Escape at Week 16

At Week 16, 12 (4.9%) subjects in the guselkumab 100 mg q4w group, 13 (5.2%) subjects in the guselkumab 100 mg q8w group, and 38 (15.4%) subjects in the placebo group met EE criteria.

Treatment failure Through Week 24

Through Week 24, 42 (5.7%) subjects met at least 1 treatment failure criterion, 13 (5.3%) subjects in the guselkumab 100 mg q4w group, 12 (4.8%) subjects in the guselkumab 100 mg q8w group, and 17 (6.9%) subjects in the placebo group. The most common reasons for meeting treatment failure criteria were initiation or increase the dose of non-biologic DMARD or oral corticosteroids over baseline for PsA (24 [3.2%] subjects), and discontinuation of study agent due to any reason (23 [3.1%] subjects).

Recruitment

In Study PSA3001, a total of 381 subjects were randomized and received at least 1 study drug administration at 86 sites in 13 countries: Australia (n=6), Malaysia (n=5), Republic of Korea (n=2), Taiwan (n=7), Czech Republic (n=5), Germany (n=5), Hungary (n=5), Poland (n=11), Russia (n=10), Spain (n=7), Ukraine (n=10), Canada (n=6), and US (n=7).

The study was initiated on 28 August 2017 when the first subject consented to participate in the study. The last study-related procedure for the 24-Week CSR was performed on 14 March 2019.

In Study PSA3002, a total of 739 subjects were randomized and received at least 1 study agent administration at 118 sites in 13 countries: Malaysia (n=5), Taiwan (n=1), Bulgaria (n=7), Czech Republic (n=7), Estonia (n=4), Latvia (n=3), Lithuania (n=4), Poland (n=15), Russia (n=25), Spain (n=9), Turkey (n=8), Ukraine (n=28), and US (n=2).

The study was initiated on 13 July 2017 when the first subject consented to participate in the study. The last study-related procedure for the 24-Week CSR was performed on 06 March 2019.

Conduct of the study

PSA3001

Database locks are scheduled at Weeks 24 and End of Study (Week 60). Study initiated on 28 August 2017. Date of data cutoff was on 14 March 2019.

Protocol Deviations

The number of subjects with MPDs through Week 24 is presented in Table 5.4.2.3

Table 5.4.2.3 Number of Subjects with Major Protocol Deviations through Week 24; Full Analysis Set (Study CNTO1959PSA3001)

Analysis set: Full Analysis Set 1	Placebo 126	Guselkumab 100 mg q8w 127	Guselkumab 100 mg q4w 128	Guselkumab Combined 255	Total 381
Subjects with major protocol deviations	16 (12.7%)	17 (13.4%)	11 (8.6%)	28 (11.0%)	44 (11.5%)
Entered but did not satisfy criteria	1 (0.8%)	3 (2.4%)	1 (0.8%)	4 (1.6%)	5 (1.3%)
Received wrong treatment or incorrect dose	1 (0.8%)	0	0	0	1 (0.3%)
Received a disallowed concomitant treatment	3 (2.4%)	1 (0.8%)	0	1 (0.4%)	4 (1.0%)
Developed withdrawal criteria but not withdrawn	0	0	0	0	0
Other	13 (10.3%)	14 (11.0%)	10 (7.8%)	24 (9.4%)	37 (9.7%)

PSA3002

Database locks were scheduled at Week 24, Week 52, and Week 112. Study initiated on 13 July 2017. Date of data cutoff was on 06 March 2019.

Protocol Deviations

The number of subjects with MPDs through Week 24 is presented in Table. 5.4.2.4

Table 5.4.2.4 Number of Subjects with Major Protocol Deviations through Week 24; Full Analysis Set 1 (Study CNTO1959PSA3002)

Analysis set: Full Analysis Set 1	Placebo 246	Guselkumab 100 mg q8w 248	Guselkumab 100 mg q4w 245	Guselkumab Combined 493	Total 739
Subjects with major protocol deviations	23 (9.3%)	18 (7.3%)	17 (6.9%)	35 (7.1%)	58 (7.8%)
Entered but did not satisfy criteria	6 (2.4%)	2 (0.8%)	3 (1.2%)	5 (1.0%)	11 (1.5%)
Received wrong treatment or incorrect dose	2 (0.8%)	3 (1.2%)	1 (0.4%)	4 (0.8%)	6 (0.8%)
Received a disallowed concomitant treatment	3 (1.2%)	2 (0.8%)	1 (0.4%)	3 (0.6%)	6 (0.8%)
Developed withdrawal criteria but not withdrawn	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Other	15 (6.1%)	12 (4.8%)	12 (4.9%)	24 (4.9%)	39 (5.3%)

Additionally, due to a programming error on the SitePad for the LEI score, the medial epicondyle humerus enthesis was included instead of the medial femoral condyle enthesis. This affected data for 10 randomized subjects prior to correction.

Resolution status at Week 24 was assessable for those subjects who had enthesitis in at least one of the 4 assessed sites at baseline, otherwise the resolution status was set to missing. Only 2 of the 10 subjects had missing post-baseline data for enthesitis due to the error and their enthesitis resolution status at Week 24 could not be assessed.

Deviation Impact Summary for PSA 3001 and PSA3002 studies

On the identification of the deviations, assessment of subject safety and whether or not it was clinically appropriate for the subject to remain in the study was carried out. The majority of subjects reported to have deviations to study entry criteria were generally detected during monitoring and based upon the safety evaluation all were allowed to continue in the study. Subjects with deviations related to concomitant medications were further evaluated to determine if they were treatment failures for the primary and major secondary analyses. In Study PSA3001, no subjects were required to be discontinued due to deviations related to safety, while in Study PSA3002, subjects with deviations related to safety and who remained under treatment when the deviation was identified were discontinued.

In summary, the deviations noted were managed to protect subject safety and overall, these deviations did not impact the integrity of the study. The MPDs were considered not to have impacted the overall study results.

Baseline data

PSA3001

Demographics

Table 5.4.2.5 Summary of Demographics at Baseline; Full Analysis Set 1 (Study CNTO1959PSA3001)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	126	127	128	255	381
Age (years)					
N	126	127	128	255	381
Mean (SD)	49.0 (11.10)	48.9 (11.52)	47.4 (11.59)	48.2 (11.55)	48.4 (11.39)
Sex					
N	126	127	128	255	381
Male	61 (48.4%)	68 (53.5%)	66 (51.6%)	134 (52.5%)	195 (51.2%)
Race					
N	126	127	128	255	381
Asian	12 (9.5%)	10 (7.9%)	7 (5.5%)	17 (6.7%)	29 (7.6%)
Native Hawaiian or other Pacific Islander	0	1 (0.8%)	0	1 (0.4%)	1 (0.3%)
White	112 (88.9%)	116 (91.3%)	121 (94.5%)	237 (92.9%)	349 (91.6%)
Not reported	2 (1.6%)	0	0	0	2 (0.5%)
Weight (kg)					
N	126	127	128	255	381
Mean (SD)	85.2 (18.76)	86.3 (19.95)	86.7 (17.70)	86.5 (18.82)	86.0 (18.78)
≤ 90	81 (64.3%)	78 (61.4%)	69 (53.9%)	147 (57.6%)	228 (59.8%)
> 90	45 (35.7%)	49 (38.6%)	59 (46.1%)	108 (42.4%)	153 (40.2%)
Height (cm)					
N	126	127	128	255	381
Mean (SD)	169.3 (9.53)	169.9 (9.35)	170.0 (9.19)	169.9 (9.25)	169.7 (9.34)
Body mass index (kg/m^2)					
N	126	127	128	255	381
Mean (SD)	29.6 (5.70)	29.9 (6.37)	29.9 (5.45)	29.9 (5.91)	29.8 (5.84)
Median	29.1	29.1	29.8	29.4	29.3
Normal (< 25)	26 (20.6%)	27 (21.3%)	26 (20.3%)	53 (20.8%)	79 (20.7%)
Overweight (≥ 25 and < 30)	48 (38.1%)	48 (37.8%)	40 (31.3%)	88 (34.5%)	136 (35.7%)
Obese (≥ 30)	52 (41.3%)	52 (40.9%)	62 (48.4%)	114 (44.7%)	166 (43.6%)

Baseline disease characteristics

Table 5.4.2.6 Summary of PsA Disease Characteristics at Baseline; Full Analysis Set 1 (StudyCNTO1959PSA3001)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	126	127	128	255	381
PsA disease duration (years)					
N	126	127	128	255	381
Mean (SD)	7.22 (7.589)	6.42 (5.910)	6.60 (6.299)	6.51 (6.097)	6.75 (6.626)
Age at PsA diagnosis (years)					
N	126	127	128	255	381
Mean (SD)	42.3 (11.63)	43.0 (12.05)	41.3 (12.47)	42.2 (12.27)	42.2 (12.04)

PsA primary subtype					
N	126	127	128	255	381
Distal interphalangeal joint involvement	9 (7.1%)	11 (8.7%)	8 (6.3%)	19 (7.5%)	28 (7.3%)
Polyarticular arthritis with absence of rheumatoid nodules	56 (44.4%)	58 (45.7%)	52 (40.6%)	110 (43.1%)	166 (43.6%)
Arthritis mutilans	0	2 (1.6%)	0	2 (0.8%)	2 (0.5%)
Asymmetric peripheral arthritis	37 (29.4%)	30 (23.6%)	43 (33.6%)	73 (28.6%)	110 (28.9%)
Spondylitis with peripheral arthritis	24 (19.0%)	26 (20.5%)	25 (19.5%)	51 (20.0%)	75 (19.7%)
Confirmed by imaging prior to screening	22 (17.5%)	23 (18.1%)	21 (16.4%)	44 (17.3%)	66 (17.3%)
Confirmed by a rheumatologist	22 (17.5%)	26 (20.5%)	25 (19.5%)	51 (20.0%)	73 (19.2%)
Subjects with history of enthesitis as recorded by a rheumatologist	34 (27.0%)	39 (30.7%)	37 (28.9%)	76 (29.8%)	110 (28.9%)
History of Dactylitis					
N	126	127	128	255	381
Subjects with history of dactylitis as recorded by a rheumatologist	50 (39.7%)	46 (36.2%)	41 (32.0%)	87 (34.1%)	137 (36.0%)
PASI score (0-72)					
N	126	127	128	255	381
Mean (SD)	7.7 (8.85)	8.4 (9.83)	9.5 (10.07)	9.0 (9.95)	8.5 (9.61)
IGA score					
N	126	127	128	255	381
Cleared (0)	7 (5.6%)	3 (2.4%)	2 (1.6%)	5 (2.0%)	12 (3.1%)
Minimal (1)	27 (21.4%)	24 (18.9%)	16 (12.5%)	40 (15.7%)	67 (17.6%)
Mild (2)	49 (38.9%)	43 (33.9%)	48 (37.5%)	91 (35.7%)	140 (36.7%)
Moderate (3)	32 (25.4%)	51 (40.2%)	49 (38.3%)	100 (39.2%)	132 (34.6%)
Severe (4)	11 (8.7%)	6 (4.7%)	13 (10.2%)	19 (7.5%)	30 (7.9%)
< 2	34 (27.0%)	27 (21.3%)	18 (14.1%)	45 (17.6%)	79 (20.7%)
≥ 2	92 (73.0%)	100 (78.7%)	110 (85.9%)	210 (82.4%)	302 (79.3%)
BASDAI score in subjects with Spondylitis and Peripheral Arthritis and BASDAI score > 0 at baseline					
N	23	24	20	44	67
Mean (SD)	6.2 (1.78)	6.2 (1.59)	5.6 (2.45)	5.9 (2.02)	6.0 (1.94)
Median	6.8	5.7	5.9	5.8	6.0
DAS28 (CRP)					
N	126	127	128	255	381
Mean (SD)	4.94 (0.988)	4.92 (1.079)	4.65 (1.058)	4.78 (1.075)	4.84 (1.048)
Median	4.98	4.91	4.53	4.82	4.86

Table 5.4.2.7 Summary of PsA Disease Characteristics for ACR Components at Baseline; Full Analysis Set 1 (Study CNTO1959PSA3001)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	126	127	128	255	381
Number of swollen joints (0-66)					
N	126	127	128	255	381
Mean (SD)	10.1 (7.07)	10.9 (9.26)	8.6 (5.82)	9.7 (7.80)	9.8 (7.56)
Median	8.0	8.0	7.0	8.0	8.0
Number of tender joints (0-68)					
N	126	127	128	255	381
Mean (SD)	19.8 (14.39)	20.2 (14.48)	17.7 (13.08)	19.0 (13.83)	19.3 (14.00)
Median	15.0	15.0	13.0	14.0	14.2
Patient's assessment of pain (VAS; 0-10cm)					
N	126	127	128	255	381
Mean (SD)	5.80 (2.223)	5.98 (2.100)	5.87 (1.953)	5.92 (2.024)	5.89 (2.090)
Patient's global assessment of disease activity (arthritis, VAS; 0-10cm)					
N	126	127	128	255	381
Mean (SD)	6.11 (2.226)	6.53 (2.005)	6.10 (2.044)	6.32 (2.032)	6.25 (2.097)
Physician's global assessment of disease activity (VAS; 0-10cm)					
N	126	127	128	255	381
Mean (SD)	6.26 (1.692)	6.22 (1.675)	6.21 (1.619)	6.21 (1.644)	6.23 (1.658)

HAQ disability index (0-3)					
N	126	127	128	255	381
Mean (SD)	1.2391 (0.66408)	1.2057 (0.59772)	1.0938 (0.65150)	1.1495 (0.62658)	1.1791 (0.63975)
Median	1.3750	1.3750	1.1250	1.2500	1.2500
CRP (mg/dL)					
N	126	127	128	255	381
Mean (SD)	1.435 (1.8874)	1.557 (2.3671)	1.139 (1.5295)	1.347 (1.9983)	1.376 (1.9602)
Median	0.787	0.663	0.571	0.631	0.666

Among the subjects with spondylitis, median BASDAI were 5.9 in the guselkumab 100 mg q4w group, 5.7 in the guselkumab 100 mg q8w group, and 6.8 in the placebo group.

Baseline BSA and PASI measurements suggested the guselkumab 100 mg q4w group had more severe psoriasis compared to the guselkumab 100 mg q8w group and the placebo group. In addition, the proportion of subjects with IGA ≥2 (mild to severe) was higher in the guselkumab 100 mg q4w group (85.9%) compared to the guselkumab 100 mg q8w group (78.7%) and placebo (73.0%). Scalp and nail psoriasis occurred more frequently at baseline in the guselkumab 100 mg q4w and 100 mg q8w groups (79.2% and 71.0%, respectively) compared with the placebo group (67.5% and 59.5%, respectively), while the frequencies of hand/foot psoriasis were comparable between the combined guselkumab group and the placebo group. Baseline nail and hand/foot psoriasis occurred more frequently in the guselkumab 100 mg q8w group (74.8% and 47.2%, respectively) compared with the guselkumab 100 mg q4w group (67.2% and 40.6%, respectively).

Relevant Medical History and Tuberculosis Screening

The most common conditions (≥5% in the overall population) reported by subjects were hypertension (38.1%), low back pain (34.1%), hyperlipidemia (18.4%), diabetes mellitus 10.2%), depression (8.1%), chronic liver disease (7.1%), and coronary artery disease (5.5%).

The distribution of study population comorbidities was generally similar across all treatment groups, with the exception of chronic liver disease: 5.5% in the guselkumab 100 mg q4w group, 10.2% in the guselkumab 100 mg q8w group, and 5.6% in the placebo group.

Prior to screening, 9 (2.4%) subjects had a known history of latent TB: 4 (1.0%) subjects were receiving treatment for latent TB at the time of the first study agent administration and 5 (1.3%) subjects had completed appropriate treatment for latent TB in the past 5 years. A total of 22 (5.8%) subjects required treatment for latent TB prior to the first study agent administration. Overall, 54.1% of subjects had a previous Bacille Calmette-Guerin vaccination.

PSA3002

Demographics

Table 5.4.2.8 Summary of Demographics at Baseline; Full Analysis Set 1 (Study CNTO1959PSA3002

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	246	248	245	493	739
Age (years)					
N	246	248	245	493	739
Mean (SD)	46.3 (11.68)	44.9 (11.89)	45.9 (11.47)	45.4 (11.68)	45.7 (11.68)
Sex					
N	246	248	245	493	739
Male	117 (47.6%)	129 (52.0%)	142 (58.0%)	271 (55.0%)	388 (52.5%)

Race					
N	246	248	245	493	739
Asian	4 (1.6%)	8 (3.2%)	3 (1.2%)	11 (2.2%)	15 (2.0%)
White	242 (98.4%)	240 (96.8%)	242 (98.8%)	482 (97.8%)	724 (98.0%)
Weight (kg)					
N	246	248	245	493	739
Mean (SD)	84.0 (19.67)	83.0 (19.31)	85.8 (19.53)	84.4 (19.45)	84.3 (19.51)
≤ 90	154 (62.6%)	160 (64.5%)	152 (62.0%)	312 (63.3%)	466 (63.1%)
> 90	92 (37.4%)	88 (35.5%)	93 (38.0%)	181 (36.7%)	273 (36.9%)
Height (cm)					
N	246	248	245	493	739
Mean (SD)	170.2 (8.97)	170.0 (9.65)	171.6 (9.35)	170.8 (9.53)	170.6 (9.35)
Body mass index (kg/m^2)					
N	246	248	245	493	739
Mean (SD)	29.0 (6.35)	28.7 (6.26)	29.1 (5.91)	28.9 (6.09)	28.9 (6.17)
Median	27.9	27.6	28.5	28.2	28.1
Normal (< 25)	67 (27.2%)	74 (29.8%)	66 (26.9%)	140 (28.4%)	207 (28.0%)
Overweight (≥ 25 and < 30)	85 (34.6%)	82 (33.1%)	83 (33.9%)	165 (33.5%)	250 (33.8%)
Obese (≥ 30)	94 (38.2%)	92 (37.1%)	96 (39.2%)	188 (38.1%)	282 (38.2%)

Table 5.4.2.9. Summary of PsA Disease Characteristics at Baseline; Full Analysis Set 1 (Study CNTO1959PSA3002)

		Guselkumab			
	Placebo	100 mg q8w	100 mg q4w	Combined	Total
Analysis set: Full Analysis Set 1	246	248	245	493	739
PsA disease duration (years)					
N	246	248	245	493	739
Mean (SD)	5.75 (5.649)	5.11 (5.523)	5.53 (5.918)	5.32 (5.721)	5.46 (5.697)
Age at PsA diagnosis (years)					
N	246	248	245	493	739
Mean (SD)	41.1 (11.90)	40.4 (11.82)	41.0 (11.20)	40.7 (11.51)	40.8 (11.64)
PsA primary subtype					
N	246	248	245	493	739
Distal interphalangeal joint involvement	13 (5.3%)	17 (6.9%)	17 (6.9%)	34 (6.9%)	47 (6.4%)
Polyarticular arthritis with absence of rheumatoid nodules	87 (35.4%)	101 (40.7%)	93 (38.0%)	194 (39.4%)	281 (38.0%)
Arthritis mutilans	2 (0.8%)	2 (0.8%)	2 (0.8%)	4 (0.8%)	6 (0.8%)
Asymmetric peripheral arthritis	45 (18.3%)	55 (22.2%)	47 (19.2%)	102 (20.7%)	147 (19.9%)
Spondylitis with peripheral arthritis	99 (40.2%)	73 (29.4%)	86 (35.1%)	159 (32.3%)	258 (34.9%)
Confirmed by imaging	96 (39.0%)	68 (27.4%)	82 (33.5%)	150 (30.4%)	246 (33.3%)
Confirmed by pelvic x-ray at screening	42 (17.1%)	25 (10.1%)	34 (13.9%)	59 (12.0%)	101 (13.7%)
Confirmed by a rheumatologist	97 (39.4%)	73 (29.4%)	82 (33.5%)	155 (31.4%)	252 (34.1%)
History of enthesitis					
N	246	248	245	493	739
Subjects with history of enthesitis as recorded by a rheumatologist	85 (34.6%)	86 (34.7%)	94 (38.4%)	180 (36.5%)	265 (35.9%)
History of Dactylitis					
N	246	248	245	493	739
Subjects with history of dactylitis as recorded by a rheumatologist	102 (41.5%)	117 (47.2%)	111 (45.3%)	228 (46.2%)	330 (44.7%)

Table 5.4.2.10 Summary of PsA Disease Characteristics for ACR Components at Baseline; Full Analysis Set 1 (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w	Guselkumab Combined	Total
Analysis set: Full Analysis Set 1	246	248	245	493	739
Number of swollen joints (0-66)					
N	246	248	245	493	739
Mean (SD)	12.3 (6.86)	11.7 (6.82)	12.9 (7.83)	12.3 (7.36)	12.3 (7.19)
Median	10.0	9.5	11.0	10.0	10.0
Number of tender joints (0-68)					
N	246	248	245	493	739
Mean (SD)	21.6 (13.06)	19.8 (11.86)	22.4 (13.54)	21.1 (12.78)	21.3 (12.87)
Median	18.0	16.0	19.0	18.0	18.0
Patient's assessment of pain (VAS; 0-10cm)					
N	246	248	245	493	739
Mean (SD)	6.28 (1.773)	6.31 (1.958)	6.15 (1.987)	6.23 (1.972)	6.25 (1.907)
Patient's global assessment of disease activity (arthritis, VAS; 0-10cm)					
N	246	248	245	493	739
Mean (SD)	6.51 (1.790)	6.53 (1.932)	6.39 (1.943)	6.46 (1.937)	6.48 (1.888)
Physician's global assessment of disease activity (VAS; 0-10cm)					
N	246	248	245	493	739
Mean (SD)	6.65 (1.490)	6.56 (1.606)	6.62 (1.538)	6.59 (1.571)	6.61 (1.544)
HAQ disability index (0-3)					
N	245	248	245	493	738
Mean (SD)	1.2949 (0.55755)	1.2848 (0.62676)	1.2490 (0.56732)	1.2670 (0.59762)	1.2763 (0.58439)
Median	1.3750	1.2500	1.2500	1.2500	1.2500
CRP (mg/dL)					
N	246	248	245	493	739
Mean (SD)	2.116 (2.6652)	2.036 (2.3528)	1.807 (2.2247)	1.922 (2.2906)	1.986 (2.4217)
Median	1.155	1.310	1.160	1.210	1.200

Baseline PsA disease characteristics were generally similar across the treatment groups and were consistent with a PsA population. The only exception was spondylitis, which occurred with higher frequency in placebo and Q4W groups than in Q8W group.The median PsA duration was 3.43 years and the majority (56.3%) of subjects had a PsA disease duration of ≥3 years.

Baseline PsA disease characteristics for these subgroups were generally consistent with that of the overall population and generally well balanced among the treatment groups.

Baseline clinical characteristics of PsA from the ACR core set of outcome measurements were indicative of subjects with PsA of moderate to severe activity and were comparable across the treatment groups; however, median CRP was slightly higher in the guselkumab 100 mg q8w group (1.310 mg/dL) compared with the guselkumab 100 mg q4w group (1.160 mg/dL) and the placebo group (1.155 mg/dL) (OC).

Baseline disease characteristics of psoriasis measurements (BSA, IGA, and PASI) were indicative of significant psoriatic skin involvement in a majority of subjects.

In the overall population, the majority of subjects reported scalp psoriasis (82.5%) followed by nail psoriasis (61.3%), and hand and/or foot psoriasis (49.0%).

Relevant Medical History and Tuberculosis Screening

The most common conditions (≥5% in the overall population) reported by subjects were lower back pain (43.2%), hypertension (37.1%), hyperlipidemia (13.7%), and diabetes mellitus (8.5%). Chronic liver disease was reported by 4.3% of subjects.

Prior to screening, 15 (2.0%) subjects had a known history of latent TB: 12 (1.6%) subjects were receiving treatment for latent TB at the time of study agent administration and 3 (0.4%) subjects had

completed appropriate treatment for latent TB in the past 5 years. A total of 75 (10.1%) subjects required treatment for latent TB prior to the first dose of study agent administration

Overall, 474 (64.1%) subjects had a previous Bacille Calmette-Guerin vaccination.

The mean baseline CRP values in study PSA3002 were 2.116 mg/dL in the placebo group, 2.036 mg/dL in the guselkumab q8w group, and 1.807 mg/dL in the guselkumab q4w arm. Since the baseline CRP distribution in study PSA3002 is not normally distributed, the mean value is subject to influence by outliers. In this case, the median may provide more reliable information. The median CRP value was slightly higher in the guselkumab q8w group (1.310 mg/dL) compared with the guselkumab q4w group (1.160 mg/dL) and the placebo group (1.155 mg/dL). Other baseline disease characteristics in study PSA3002, including ACR components of swollen and tender joint counts, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, and HAQ-DI, were comparable across treatment groups. Further, composite measures of baseline disease activity, including median Psoriatic Arthritis Disease Activity Score (PASDAS), Group of Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Score, (GRACE) index, mCPDAI, and DAPSA scores, were also comparable across the treatment groups.

All planned analyses included screening CRP (<2 or ≥2 mg/dL) as a stratification factor in the CMH test or as an explanatory factor in ANCOVA. To further address the Assessor's question, a new sensitivity analysis was done to include log (baseline CRP +1) as a continuous covariate in the logistic regression model to analyze the primary endpoint of ACR 20 as well as change from baseline in modified vdH-S score at Week 24. These analyses confirmed the robustness of the results.

Prior and Concomitant Therapies

Study PSA3001

Prior Anti-TNFα Agents

At baseline, 31.0% of subjects had prior exposure to up to 2 anti-TNFα agents and prior exposure to anti-TNFα agents was balanced across the treatment groups. Among subjects with prior exposure to anti-TNFα agents, 37.3% discontinued anti-TNFα agents due to inadequate responses and 62.7% discontinued for other reasons including AE accurrence (below 10% for each treatment groups) and financial reasons (from 25-35%in each treatment groups). The most frequently used anti-TNFα agents among these subjects were etanercept (33.9%) and adalimumab (31.4%).

Prior Non-biologic PsA Medications

The majority (91.3%) of subjects had received prior non-biologic treatments, including DMARDs (90.3%), immunosuppressives (4.5%), or apremilast (3.1%). In addition, 41.5% of the subjects had used systemic corticosteroids and 85.3% of the subjects had taken NSAIDs previously.

Prior to baseline, the most commonly used DMARD was MTX (80.8%), followed by SSZ (29.4%), LEF (17.6%), and HCQ (1.6%). The median maximal MTX dose in the 3 months prior to baseline was 15.0 mg/week. The majority of subjects with prior exposure to MTX (68.5%) continued use of MTX at baseline.

Selected Baseline Medications for PsA

At baseline, 64.8% of the overall study population were receiving DMARDs, including 55.4% of subjects on MTX (median dose 15.0 mg/week), 5.5% on SSZ (median dose 2.0 g/day), and 3.9% on LEF (median dose 20 mg/day). In addition, 14.2% of subjects in the overall population were receiving oral corticosteroids (median dose 5.0 mg/day prednisone or equivalent) and 57.0% were receiving NSAIDs for PsA at baseline.

The proportions of subjects receiving these medications at baseline were well balanced across treatment groups.

Concomitant Medication Modifications at Early Escape

At Week 16, 31 (8.1%) subjects met EE criteria and were allowed to initiate or increase the dose of their permitted concomitant medications up to the maximum allowed dose as selected by the investigator: 3 (2.3%) subjects in guselkumab group 100 mg q4w, 4 (3.1%) subjects in the guselkumab 100 mg q8w group, and 24 (19.0%) subjects in the placebo group. In guselkumab Q8W group and in the placebo group one of the 4 subjects and 13 of the 24 subjects, respectively, elected to adjust their concomitant medication for PsA.

Study PSA3002

Prior and Concomitant Therapies

Prior Medications or Therapies for PsA

The huge majority of subjects with prior PsA medication received NSAIDs (93.2%), followed by DMARDs (90.8%) and systemic corticosteroids (47.0%)

The majority of subjects in the study had prior exposure to MTX (85.0%) and the proportion was well balanced across the treatment groups. The majority of subjects (70.5%) continued use of MTX at BL.

Prior Medications or Therapies for Psoriasis

The proportion of subjects with prior exposure to medications and therapies for psoriasis was 64.5% in the guselkumab 100 mg q4w group, 62.5% in the guselkumab 100 mg q8w group, and 63.4% in the placebo group. The type of medications or therapies used and length of exposure was well balanced across the treatment groups. As prior psoriasis medication, topical agent were used in 61.3% of the patients followed by UVB (9.5%) and PUVA (5.8%)

Selected Baseline Medications for PsA

For subjects receiving non-biologic DMARDs at baseline, the majority of subjects were receiving MTX (59.9%), followed by LEF (4.7%), SSZ (4.2%), and HCQ (0.4%). The median dose of MTX was 15.0 mg/week and was the same across the treatment groups. The median dose of oral corticosteroids (prednisone or equivalent dose) was 5.0 mg/day in both guselkumab groups compared with 10.0 mg/day in the placebo group.

Concomitant Medication Modifications at Early Escape

At Week 16, 63 (8.5%) subjects met EE criteria and were allowed to initiate or increase the dose of 1 of the permitted concomitant medications up to the maximum protocol-allowed dose as selected by the investigator. Of these subjects, 27 (3.7%) subjects initiated or increased dose of permitted concomitant medications.

Numbers analysed

In Study PSA3001, a total of 381 subjects were randomized and treated: 128 in the guselkumab 100 mg q4w group, 127 in the guselkumab 100 mg q8w group, and 126 in the placebo group.

Analysis sets used in Study PSA3001 are presented in Table 5.4.2.11

Table 5.4.2.11 Number of Subjects in Each Analysis Set; Randomized Subjects (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w	Combined	Total
Analysis Set: Subjects Randomized	126	128	128	256	382
Subjects Not Treated	0	1 (0.8%)	0	1 (0.4%)	1 (0.3%)
Full Analysis Set 1	126 (100.0%)	127 (99.2%)	128 (100.0%)	255 (99.6%)	381 (99.7%)
Per-Protocol Analysis Set	123 (97.6%)	123 (96.1%)	127 (99.2%)	250 (97.7%)	373 (97.6%)
Safety Analysis Set	126 (100.0%)	127 (99.2%)	128 (100.0%)	255 (99.6%)	381 (99.7%)
Pharmacokinetics Analysis Set	0	126 (98.4%)	128 (100.0%)	254 (99.2%)	254 (66.5%)
Immunogenicity Analysis Set	0	126 (98.4%)	128 (100.0%)	254 (99.2%)	254 (66.5%)

In Study PSA3002, a total of 741 subjects were randomized and 739 subjects were treated: 245 in the guselkumab 100 mg q4w group, 248 in the guselkumab 100 mg q8w group, and 246 in the placebo group.

Table.5.4.2.12 Number of Subjects in Each Analysis Set; Randomized Subjects (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w	Combined	Total
Analysis Set: Subjects Randomized	247	248	246	494	741
Subjects Not Treated	1 (0.4%)	0	1 (0.4%)	1 (0.2%)	2 (0.3%)
Full Analysis Set 1	246 (99.6%)	248 (100.0%)	245 (99.6%)	493 (99.8%)	739 (99.7%)
Full Analysis Set 1 for Structural Damage (Read Campaign 1)	246 (99.6%)	248 (100.0%)	245 (99.6%)	493 (99.8%)	739 (99.7%)
Per-Protocol Analysis Set	237 (96.0%)	246 (99.2%)	241 (98.0%)	487 (98.6%)	724 (97.7%)
Safety Analysis Set	246 (99.6%)	248 (100.0%)	245 (99.6%)	493 (99.8%)	739 (99.7%)
Pharmacokinetics Analysis Set	0	248 (100.0%)	244 (99.2%)	492 (99.6%)	492 (66.4%)
Immunogenicity Analysis Set	0	247 (99.6%)	243 (98.8%)	490 (99.2%)	490 (66.1%)

Outcomes and estimation

PSA3001

Improvement in Signs and Symptoms of Psoriatic Arthritis

ACR Response

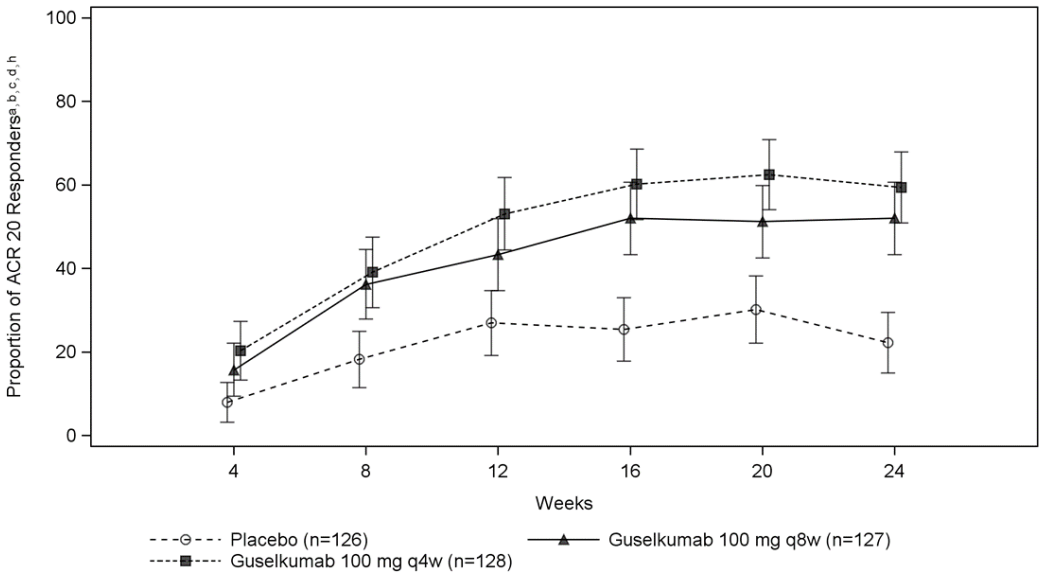
Table 5.4.2.13 : Number of subjects who achieved an ACR 20, ACR 50, and ACR 70 response at Week 24 and Week 16; full analysis set in study CNTO1959PSA3001

	Placebo	Guselkumab	
		100 mg q8w	100 mg q4w
Full Analysis Set 1	126	127	128
ACR 20 at Week 24			
Subjects in response[a]	28 (22.2%)	66 (52.0%)	76 (59.4%)
Adjusted (nominal) p-value[b]		< 0.001 (< 0.001)	< 0.001 (< 0.001)
ACR 20 at Week 16			
Subjects in response[a]	32 (25.4%)	66 (52.0%)	77 (60.2%)
Adjusted (nominal) p-value[b]		< 0.001 (< 0.001)	< 0.001 (< 0.001)
ACR 50 at Week 24			
Subjects in response[a]	11 (8.7%)	38 (29.9%)	46 (35.9%)
Adjusted (nominal) p-value[b]		< 0.001 (< 0.001)	< 0.001 (< 0.001)
ACR 50 at Week 16			
Subjects in response[a]	16 (12.7%)	29 (22.8%)	34 (26.6%)
Adjusted (nominal) p-value[b]		0.086 (0.036)	0.006 (0.006)
ACR 70 at Week 24			
Subjects in response[a]	7 (5.6%)	15 (11.8%)	26 (20.3%)
Adjusted (nominal) p-value[b]		0.086 (0.069)	< 0.001 (<0.001)

[a] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[b] The graph based multiple comparison procedure "gMCP" package in the R software was used to calculate the adjusted p-values based on the multiplicity control testing procedure. Nominal p-values are given in parentheses and are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and prior exposure to anti-TNFα agents (yes/no).

ACR Response Over Time

Figure 5.4.2.3 Line Plot of the Number of Subjects Achieving ACR 20 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)



[a]Per the composite estimand subjects either have an observed ACR 20 response status or met a Treatment Failure (TF) criterion.
[b]Defined as observed responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed.
[c]Subjects with missing data at a visit are assumed to be non-responders at that visit.
[d]The confidence intervals are based on the Wald statistic.

Figure 5.4.2.4 Line Plot of the Number of Subjects Achieving ACR 50 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)

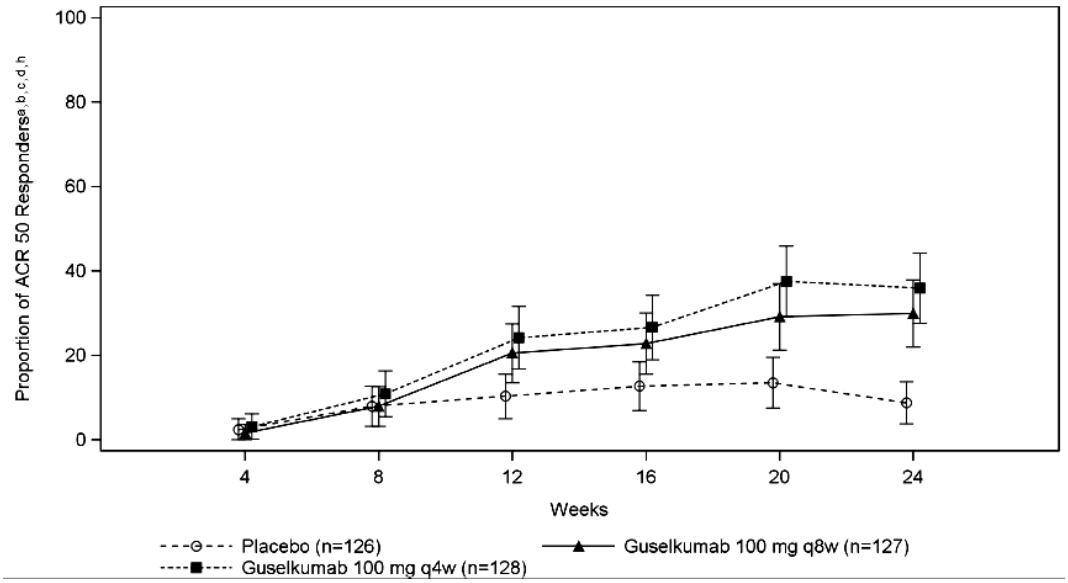
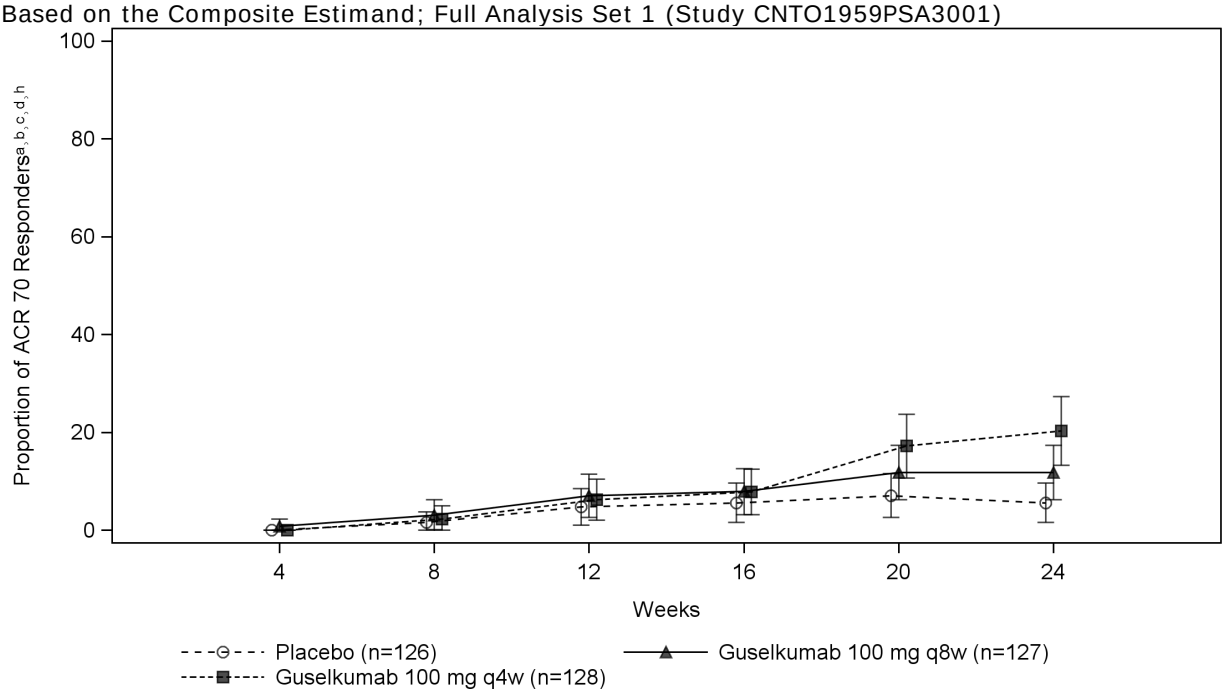


Figure 5.4.2.5 Line Plot of the Number of Subjects Achieving ACR 70 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)



[a]Per the composite estimand subjects either have an observed ACR 20 response status or met a Treatment Failure (TF) criterion.
[b]Defined as observed responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed.
[c]Subjects with missing data at a visit are assumed to be non-responders at that visit.

Subgroup Analyses for ACR20 response (PSA3001)

Subgroup analyses were carried out for ACR 20 response at Week 24 over subgroups defined by demography, baseline disease characteristics, and prior and concomitant use of medications for PsA. A consistent treatment benefit was observed for ACR 20 response in each of the two guselkumab dose groups among the subgroups defined by baseline demographics, baseline disease characteristics, and

prior and baseline medication use. For the majority of baseline demography and disease characteristics subgroups, the lower bound of the 95% CI of the difference in proportion of ACR 20 responders was above 0 for each guselkumab treatment compared with placebo, in favor of guselkumab.

Improvement over placebo was consistently observed for ACR 20 response at Week 24 in each of the 2 guselkumab dose groups in the subgroups defined by prior anti-TNFα agent exposure. In these subgroups, the lower bound of the 95% CI of the odds ratio was above 1 and the lower bound of the 95% CI of the difference in proportion of ACR 20 responders was above 0 for each guselkumab treatment compared with placebo, in favor of guselkumab. Improvement over placebo was also observed in subjects who had prior inadequate response to anti-TNFα agents.

For each of the 2 guselkumab dose regimens, the treatment effect was comparable among subjects with or without prior exposure to anti-TNFα agents.

Sensitivity analyses for ACR20 response (PSA3001)

To test the robustness of the above primary analysis, the following prespecified sensitivity and supplementary analyses were performed:

- An analysis similar to the above primary analysis but based on the treatment policy estimand with missing data imputed by MI where all observed data collected for the endpoint were used and no treatment failure rules were applied (both nominal $p<0.001$).
- Tipping point analyses based on the treatment policy estimand with missing data imputed by MI where all observed data collected for the endpoint were used and no treatment failure rules were applied. One subject in the guselkumab 100 mg q4w group, 4 subjects in the guselkumab 100 mg q8w group, and 8 subjects in the placebo group had data missing, and the result did not tip under any assumptions in all missing data imputation scenarios penalizing guselkumab and/or favoring placebo .
- An analysis similar to the above primary analysis but based on the alternative composite estimand (both nominal $p<0.001$).
- An analysis similar to the above primary analysis but based on the per-protocol estimand (both nominal $p<0.001$).

Disease Activity Index Score 28 (DAS28) Response

Table 5.4.2.14 Summary of the Change from Baseline in DAS 28 (CRP) Score at Week 24 Based on the Composite Estimand Using MI and an ANCOVA Model; Full Analysis Set 1 (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in DAS28 (CRP)[a,h]			
Subjects evaluable[b]			
N	126	126	128
Mean (SD)	-0.72 (1.015)	-1.44 (1.144)	-1.53 (1.060)
Median	-0.46	-1.36	-1.50
Range	(-4.0; 1.8)	(-4.5; 1.2)	(-4.4; 0.5)
IQ range	(-1.26; 0.00)	(-2.06; -0.61)	(-2.30; -0.76)
All subjects (including those with imputed data)[a,c,h]			
N	126	127	128
Mean (SE)[d]	-0.72 (0.090)	-1.44 (0.101)	-1.53 (0.094)
Model Based Estimates of the Mean Change[a,c,h]			
LSMean (95% CI)[e]	-0.70 (-0.89, -0.51)	-1.43 (-1.61, -1.24)	-1.61 (-1.80, -1.42)
LSMean difference (95% CI)		-0.73 (-0.98, -0.48)	-0.91 (-1.16, -0.66)
p-value[f]		< 0.001	< 0.001

As early as the first evaluation at Week 4, a greater reduction in DAS28 (CRP) score from baseline was observed in the guselkumab q8w and q4w groups compared with the placebo group. The treatment effect increased over time and through Week 24 for both guselkumab q8w and q4w groups versus placebo. At Week 24, a significantly greater reduction from baseline in DAS28 (CRP) score was observed in both guselkumab groups, compared with placebo (both global adjusted $p<0.001$.

At Week 24, the proportion of subjects achieving a DAS28 (CRP) good or moderate response was 70.9% and 76.6% in the guselkumab q8w and q4w groups, respectively, compared with 44.4% (both nominal $p<0.001$) in the placebo group.

At Week 24, DAS28 (CRP) remission was observed for a greater proportion of subjects in the guselkumab q8w and q4w groups (23.6% and 35.9%, respectively) compared with the placebo group (12.7%; nominal $p<0.001$ and $p=0.025$, respectively.

Table 5.4.2.15 Number of Subjects Achieving DAS 28 (CRP) Remission by Visit Through Week 24 in Evaluable Subjects Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Subjects evaluable for DAS28 (CRP) remission[a]			
Week 4	124	120	128
Subjects with DAS28 (CRP) remission[b,h]	4 (3.2%)	10 (8.3%)	10 (7.8%)
Week 8	119	124	127
Subjects with DAS28 (CRP) remission[b,h]	10 (8.4%)	14 (11.3%)	15 (11.8%)
Week 12	122	123	127
Subjects with DAS28 (CRP) remission[b,h]	12 (9.8%)	28 (22.8%)	28 (22.0%)
Week 16	120	122	124
Subjects with DAS28 (CRP) remission[b,h]	10 (8.3%)	25 (20.5%)	33 (26.6%)
Week 20	118	121	126
Subjects with DAS28 (CRP) remission[b,h]	22 (18.6%)	32 (26.4%)	47 (37.3%)
Week 24	118	122	127
Subjects with DAS28 (CRP) remission[b,h]	17 (14.4%)	30 (24.6%)	46 (36.2%)

[a] Subjects have an observed DAS 28 (CRP).
[b] Defined as responders regardless of Treatment Failure (TF).
[h] The DAS 28 (CRP) score is calculated based on the tender joints (28), swollen joints (28), patient's global assessment of disease activity, and CRP. DAS 28(CRP) remission is defined as DAS 28 (CRP) value <2.6 at the analysis visit.

Summary of the Change from Baseline in DAS 28 (CRP) Score at Week 24 Based on the Composite Estimand Using MI and an ANCOVA Model; Full Analysis Set 1 (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in DAS28 (CRP)[a,h]			
Subjects evaluable[b]			
N	126	126	128
Mean (SD)	-0.72 (1.015)	-1.44 (1.144)	-1.53 (1.060)
Median	-0.46	-1.36	-1.50
Range	(-4.0; 1.8)	(-4.5; 1.2)	(-4.4; 0.5)
IQ range	(-1.26; 0.00)	(-2.06; -0.61)	(-2.30; -0.76)
All subjects (including those with imputed data)[a,c,h]			
N	126	127	128
Mean (SE)[d]	-0.72 (0.090)	-1.44 (0.101)	-1.53 (0.094)
Model Based Estimates of the Mean Change[a,c,h]			
LSMean (95% CI)[e]	-0.70 (-0.89, -0.51)	-1.43 (-1.61, -1.24)	-1.61 (-1.80, -1.42)
LSMean difference (95% CI)		-0.73 (-0.98, -0.48)	-0.91 (-1.16, -0.66)
p-value[f]		< 0.001	< 0.001

In study PSA3001, the proportions of subjects who achieved a DAS28 (CRP) LDA (defined as DAS28 (CRP) score ≤3.2 or remission) at Week 24 were 43.3% and 57.8% in the guselkumab 100 mg q8w and q4w groups, respectively compared with 17.5% in the placebo group (both nominal p<0.001). The proportions of subjects who achieved a DAS28 (CRP) remission (defined as DAS28 (CRP) score <2.6) at Week 24 were 23.6% and 35.9% in the guselkumab 100 mg q8w and q4w groups, respectively compared with 12.7% in the placebo group (nominal p=0.025 and p<0.001, respectively).

At Week 52, the proportions of subjects who achieved DAS28 (CRP) LDA or remission were 65.2%, 73.2%, and 61.2% in the guselkumab 100 mg q8w, q4w, and placebo→guselkumab 100 mg q4w groups, respectively. The proportions of subjects who achieved DAS28 (CRP) remission at Week 52 were 43.8%, 56.1%, and 37.9% in the guselkumab 100 mg q8w, q4w, and placebo→guselkumab 100 mg q4w groups, respectively.

Among those subjects who achieved DAS28 (CRP) LDA or remission and DAS28 (CRP) remission at Week 24 with evaluable data at Week 52, the proportions of subjects who maintained DAS28 (CRP) LDA or remission and DAS28 (CRP) remission at Week 52 were 96.2% and 75.0%, respectively, in the guselkumab 100 mg q8w group and 91.8% and 86.7%, respectively, in the guselkumab 100 mg q4w group.

The greater proportion of subjects who achieved DAS28 (CRP) LDA or remission in both guselkumab dose groups at Week 24 in study PSA3002 is clinically meaningful, as is the high proportion of subjects who maintained this response from Week 24 to Week 52. This is further supported by the substantially greater proportions of subjects who achieved DAPSA LDA or remission in both Q4W and Q8W dosing groups in study PSA3002.

Dactylitis

At baseline, 37.4% (n=142) of subjects randomized were diagnosed with dactylitis and included in the efficacy analyses pertaining to dactylitis.

At Week 24, numerically greater proportions of subjects in the guselkumab 100 mg q4w group (63.2%, nominal p=0.212) and the guselkumab 100 mg q8w group (65.3%, nominal p=0.088) achieved dactylitis resolution compared to the placebo group (49.1%) among the subjects diagnosed with dactylitis at BL.

At Week 24, a numerically greater reduction from baseline in dactylitis score was observed in the guselkumab 100 mg q4w group (LSmean change from baseline: −5.82, nominal p=0.225) and the guselkumab 100 mg q8w group (LSmean change from baseline: −6.11, nominal p=0.121) compared to the placebo group (LSmean change from baseline: −4.30.)

Enthesitis

At baseline, 222 (58.3%) of subjects randomized were diagnosed with enthesitis and included in the efficacy analyses pertaining to enthesitis.

At Week 24, 47.9% of subjects in the guselkumab 100 mg q4w group and 40.3% of subjects in the guselkumab 100 mg q8w group achieved enthesitis resolution compared to 27.3% of subjects in the placebo group (nominal p=0.013 and p=0.094, respectively).

At Week 24 LSmean change from baseline in LEI scores were −1.75 in the guselkumab 100 mg q4w group and −1.35 in the guselkumab 100 mg q8w group compared to −1.01 in the placebo group (nominal p=0.004 and nominal p=0.185, respectively.

As preplanned, efficacy data for both enthesitis and dactylitis endpoints were pooled with data from study PSA3002 to improve precision with increased the sample size. Results from the analyses of the pooled data are reported in Analysis performed across trials subsection.

Other Measures of (PsA) Disease Activity

In general, greater improvement from baseline or greater proportions of subjects with a response were observed in the guselkumab 100 mg q8w and q4w groups compared with the placebo group for other measures of disease activity at Week 24, including DAPSA, PASDAS, MDA, VLDA, GRACE, and PsARC.

Table 5.4.2.16: Summary of Results for Disease Activity Measures; Full Analysis set in Study CNTO1959PSA3001

	Placebo	Guselkumab	
		100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in DAPSA index			
N[a]	126	126	128
LSMean (95% CI)[b]	-10.749 (-13.396, -8.102)	-21.332 (-23.977, -18.688)	-20.621 (-23.251, -17.992)
p-value[b]		< 0.001	< 0.001
Change from baseline in PASDAS			
N[a]	125	125	127
LSMean (95% CI)[b]	-0.959 (-1.212, -0.707)	-2.124 (-2.376, -1.871)	-2.407 (-2.657, -2.156)
p-value[b]		< 0.001	< 0.001
Minimal Disease Activity (MDA)			
N	126	127	128
Subjects with MDA response[c]	14 (11.1%)	29 (22.8%)	39 (30.5%)
p-value[d]		0.012	< 0.001
Very Low Disease Activity (VLDA)			
N	126	127	128
Subjects with VLDA response[c]	2 (1.6%)	5 (3.9%)	12 (9.4%)
p-value[d]		0.447[e]	0.007
Change from baseline in GRACE Index			
N[a]	125	125	127
LSMean (95% CI)[b]	-0.854 (-1.122, -0.586)	-2.368 (-2.636, -2.099)	-2.735 (-3.001, -2.468)
p-value[b]		< 0.001	< 0.001
PsARC response			
N	126	127	128
Subjects in response[c]	39 (31.0%)	76 (59.8%)	93 (72.7%)
p-value[d]		< 0.001	< 0.001

[a] Subjects either have an observed change from baseline or response at this visit or met TF criteria prior to this visit.
[b] The LS mean and nominal p-values are based on the MMRM analysis.
[c] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[d] The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and prior exposure to anti-TNFα agents (yes/no).
[e] p-value calculated using the Fisher's exact test.
DAPSA=Disease Activity Index for Psoriatic Arthritis; GRACE= GRAPPA Composite Score; PASDAS=Psoriatic Arthritis Disease Activity Score; PsARC=Psoriatic Arthritis Responder Criteria;

Patient proportions achieving low disease activity or remission based on DAPSA criteria or minimal disease activity (MDA) increased further from Week 24 through Week 52 in both dosing regimen.

In Study PSA3001 proportions of patients achieving low disease activity and /or remission based on DAPSA or DAS28 criteria was somewhat lower in Q8W group compared to Q4W group, and this difference was maintained through Week 52. DAPSA LDA or remission rates in Q8W group were 42.6% and 59.8% at Week 24 and Week52, respectively and in Q4W group were 50.4% and 62.6% at Week24 and Week52, respectively (Table TEFDAPSA02 in PSA3001/W60CSR). DAS28 remission rates in Q8W group were 24.6% and 43.8% at Week 24 and Week 52, respectively and in Q4W group were 36.8% and 56.1% at Week 24 and Week 52, respectively. (Table TEFDAS03 in PSA3001/W60CSR). In Study PSA3002, however, CRP and DAPSA remission/LDA rates as well as their changes through Week 52 were similar for the two guselkumab dosing regimens. Namely, DAPSA LDA or remission rates at Week 24 were 40.3% and 36.8% for Q8W and Q4W groups, respectively. At Week52, 55.6% and 55.1% DAPSA LDA or remission rates were observed for Q8W and Q4W groups, respectively. (Table TEFDAPSA02 in

PSA3002/W52CSR). DAS28 remission rates TEFDAS03 in PSA3002/W52CSR). DAS28 remission rates at Week 24 were 25.6% and 24.4% for Q8W andQ4W groups, respectively. At Week52, 39.7% and 39.6% DAS28 or remission rates were observed for Q8W and Q4W groups, respectively.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

At baseline, 19.7% (75/381 overall) of subjects presented with the PsA subset of spondylitis with peripheral arthritis as their primary arthritic presentation as judged by the investigator. Among these subjects, a greater mean reduction (SD) from baseline in BASDAI at Week 24 was observed in the guselkumab q8w group (-2.630 (2.4939)) compared with the placebo group (-0.881 (1.5480), nominal p=0.004), and a numerically greater reduction was observed for the guselkumab q4w group (-1.837 (2.0792), nominal p=0.067).

Among the 17.3% (66/381) subjects with spondylitis and peripheral arthritis at baseline and imaging confirmation at screening, a greater mean reduction from baseline (SD) in BASDAI at Week 24 was observed for both the guselkumab q8w (-2.619 (2.5871)) and q4w groups (-2.189 (1.9079)) compared with the placebo group (-0.929 (1.6007), nominal p=0.007 and p=0.038, respectively.).

Higher BASDAI scores indicate greater disease severity and a score decrease of ≥50% or ≥2 points from baseline is considered clinically meaningful.39 For the threshold response of ≥50% improvement from baseline (a prespecified analysis), studies PSA3001 and PSA3002 show similar results for the two guselkumab dose regimens. At Week 24 in study PSA3001, among subjects with the primary PsA subtype of spondylitis and peripheral arthritis and BASDAI score>0 at baseline, 42% and 35% of subjects in the guselkumab 100 mg q8w and q4w groups, respectively, met the 50% threshold, compared to 13% of subjects in the placebo group (Mod5.3.5.1/PSA3001/W24CSR/AttTEFBASDAI09).

In the 23 subjects who were anti-TNFα experienced, all of whom were in study PSA3001, 3 of 7 subjects (43%) in the guselkumab 100 mg q8w group and 2 of 5 subjects (40%) in the guselkumab 100 mg q4w group, and none of the subjects in the placebo group achieved BASDAI 50.

In the small number of subjects (n=23) that were anti-TNFα experienced in study PSA3001, placebo-treated subjects showed a much smaller change from baseline BASDAI score at Week 24 than did the guselkumab-treated subjects. Additionally, the anti- TNFα-experienced placebo-treated subjects showed a smaller mean change from baseline than did the anti-TNFα-naïve placebo-treated subjects

Improvement in Skin Disease

Investigator's Global Assessment of Psoriasis

At baseline, 82 (64.6%) subjects in the guselkumab 100 mg q8w group, 89 (69.5%) subjects in the guselkumab 100 mg q4w group, and 78 (61.9%) subjects in placebo group had ≥3% BSA of psoriatic involvement and an IGA score ≥2 at baseline. IGA response rates by Week 24 are presented in Table 5.4.2.17

Table 5.4.2.17. Number of Subjects Achieving an Investigator Global Assessment (IGA) Score of 0 (Cleared) or 1 (Minimal), and ≥ 2 Grade Reduction from Baseline at Week 24, Based on the Composite Estimand; Full Analysis Set 1 Among the Subjects with **≥3%** Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score **≥2** (mild) at Baseline (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects with ≥3% Body Surface Area (BSA) Psoriatic Involvement and an IGA score of ≥2 (mild) at Baseline	78	82	89
Subjects evaluable for IGA response at Week 24[a]	78	81	89
Subjects with IGA response[b,h]	12 (15.4%)	47 (58.0%)	67 (75.3%)
All subjects (including those with imputed data)	78	82	89
Subjects with IGA response[b,c,h]	12 (15.4%)	47 (57.3%)	67 (75.3%)
% Difference (95% CI)[d]		42.0 (28.9, 55.1)	60.0 (48.3, 71.8)
p-value[e]		< 0.001	< 0.001

[a]Subjects either have an observed IGA response status or met a Treatment Failure (TF) criterion.
[b]Defined as observed responders who had not met any TF criteria prior to Week 24.
[c]Subjects with missing data are assumed to be non-responders.
[d]The confidence intervals are based on the Wald statistic.
[e]The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and prior exposure to anti-TNFα agents (yes/no).

Psoriasis Area and Severity Index

Table 5.4.2.18 : Numbers of Subjects who Achieved an PASI 50, PASI 75, PASI 90, and PASI 100 Response at Week 24; Full Analysis Set 1, Subjects with ≥3% Body Surface Area (BSA) of Psoriatic Involvement and an IGA score ≥2 (Mild) at Baseline in Study CNTO1959PSA3001

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1[a]	78	82	89
PASI 50			
Subjects in response[b]	26 (33.3%)	72 (87.8%)	85 (95.5%)
p-value[c]		< 0.001	< 0.001
PASI 75			
Subjects in response[b]	11 (14.1%)	62 (75.6%)	77 (86.5%)
p-value[c]		< 0.001	< 0.001
PASI 90			
Subjects in response[b]	9 (11.5%)	41 (50.0%)	56 (62.9%)
p-value[c]		< 0.001	< 0.001
PASI 100			
Subjects in response[b]	5 (6.4%)	21 (25.6%)	40 (44.9%)
p-value[c]		< 0.001	< 0.001

[a] Includes only subjects who had ≥3% BSA of psoriatic involvement and an IGA score ≥2 (mild) at baseline in the Full Analysis Set 1.
[b] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[c] The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and prior exposure to anti-TNFα agents (yes/no).

Subjects Achieving Both PASI 75 and ACR 20 Response

Table 5.4.2.19 :Number of Subjects Achieving Both PASI 75 and ACR 20 Responses by Visit Through Week 24, Based on the Composite Estimand; Full Analysis Set 1 Among the Subjects with **≥3%** Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score **≥2** (mild) at Baseline (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects Who had ≥3% Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score ≥2 (mild) at Baseline	78	82	89
Week 16			
Subjects evaluable for PASI 75 and ACR 20 responses[a]	76	81	87
Subjects with PASI 75 and ACR 20 responses[b,h]	5 (6.6%)	29 (35.8%)	43 (49.4%)
All subjects (including those with imputed data)	78	82	89
Subjects with PASI 75 and ACR 20 responses[b,c,h]	5 (6.4%)	29 (35.4%)	43 (48.3%)
% Difference (95% CI)[d]		29.1 (17.5, 40.7)	41.8 (30.2, 53.4)
p-value[e]		< 0.001	< 0.001
Week 24			
Subjects evaluable for PASI 75 and ACR 20 responses[a]	78	81	89
Subjects with PASI 75 and ACR 20 responses[b,h]	5 (6.4%)	33 (40.7%)	47 (52.8%)
All subjects (including those with imputed data)	78	82	89
Subjects with PASI 75 and ACR 20 responses[b,c,h]	5 (6.4%)	33 (40.2%)	47 (52.8%)
% Difference (95% CI)[d]		33.7 (21.9, 45.5)	46.7 (35.1, 58.3)
p-value[e]		< 0.001	< 0.001

Improvement in Physical Function

Physical function was assessed using the HAQ-DI questionnaire. The population in this study had mild to moderate disability as indicated by the median baseline HAQ-DI score of 1.250 across all treatment groups.

Table 5.4.2.20 Summary of the Change from Baseline in HAQ-DI Score at Week 24 Based on the Composite Estimand Using MI, Full Analysis Set 1 (Study CNTO1959PSA3001)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in HAQ-DI[a,h]			
Subjects evaluable[b]			
N	126	127	128
Mean (SD)	-0.0873 (0.48638)	-0.3248 (0.56371)	-0.3652 (0.45723)
Median	0.0000	-0.2500	-0.2500
Range	(-1.625; 2.000)	(-1.875; 1.750)	(-1.750; 0.750)
IQ range	(-0.3750; 0.1250)	(-0.7500; 0.0000)	(-0.6250; 0.0000)
All subjects (including those with imputed data)[a,c,h]			
N	126	127	128
Mean (SE)[d]	-0.0873 (0.04333)	-0.3248 (0.05002)	-0.3652 (0.04041)
Model Based Estimates of the Mean Change[a,c,h]			
LSMean (95% CI)[e]	-0.0743 (-0.1605, 0.0119)	-0.3225 (-0.4082, -0.2369)	-0.3968 (-0.4825, -0.3112)
LSMean difference (95% CI)		-0.2483 (-0.3640, -0.1325)	-0.3226 (-0.4385, -0.2066)
p-value[f]		< 0.001	< 0.001

[a]Defined as the change from baseline using observed data or 0 (no improvement) if a subject met Treatment Failure (TF)
criteria prior to Week 24.
[b]Subjects either have an observed change from baseline at this visit or met TF criteria prior to this visit.
[c]Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[d]The average of the mean, taken over all the MI data sets, is presented. The variance of the mean is the weighted sum of the average within-imputation variance and the between-imputation variance.

The mean reduction from baseline was numerically greater in the guselkumab q4w group compared with the q8w group. Improvements in HAQ-DI were observed as early as Week 4 in subjects receiving guselkumab. The improvement was numerically greater in both guselkumab groups compared with the placebo group at all visits from Week 4 through Week 24.

Greater proportions of subjects in the guselkumab q8w and q4w groups were observed to achieve a clinically meaningful HAQ-DI response (defined as ≥0.35 improvement in HAQ-DI from baseline) at Week 16 as well as at Week 24 (57.3% and 50.9% for Q4W and Q8W, respectively) compared with the placebo group (29.1%; nominal p=0.001 and p<0.001) respectively at Week 24.

Improvement in Health-related Quality of Life

Improvement in Health-related quality of life was assessed using SF-36 PCS and MSC scores, FACIT-Fatigue scores, and PROMIS-29 scores. At week 24, significant (SF-36 PCS,) or numeric difference was observed for both dosing schemes compared to PBO. Proportion of subjects reaching a clinically meaningful improvement on the above mentioned Health quality of life endpoints was also assessed, but no equivocal conclusion can be drawn from it.

MDA and VLDA

Minimal disease activity (MDA) was considered achieved if 5 of the following 7 criteria were met: tender joint count ≤1; swollen joint count ≤1; PASI ≤1; patient pain VAS score of ≤15; patient global disease activity VAS (arthritis and psoriasis) score of ≤20; HAQ ≤0.5; and LEI ≤1.
Very Low Disease Activity (VLDA) was considered achieved if all 7 criteria were met. Both MDA and VLDA were evaluated at Weeks 0, 16, and 24.

MDA Criteria Through Week 24

The proportion of subjects achieving MDA was higher at both Week 16 and Week 24 in the guselkumab 100 mg q4w (18.0% and 30.5%; nominal p=0.010 and p<0.001, respectively) and guselkumab 100 mg q8w (15.7% and 22.8%, nominal p=0.034 and p=0.012, respectively) groups compared with the placebo group (7.1% and 11.1%, respectively)

VLDA Criteria Through Week 24

The proportions of subjects who met VLDA criteria at Week 16 were low and comparable among all treatment groups. At Week 24, 12 (9.4%) subjects in the guselkumab 100 mg q4w group and 5 (3.9%) subjects in the guselkumab 100 mg q8w group achieved VLDA compared with 2 (1.6%) subjects in the placebo group (nominal p=0.007 and p=0.447, respectively)

Efficacy and Pharmacokinetics

Exposure-Response analyses are discussed in detail in the PK/PD modelling subsection of this AR.

Efficacy and Immunogenicity

The incidence of antibodies to guselkumab across all guselkumab treatment groups through Week 24 was 2.0%. Among the 5 subjects who were positive for antibodies to guselkumab, 3 (60.0%) achieved an ACR 20 response compared with 55.8% of subjects who were negative for antibodies to guselkumab. None of the subjects who were positive for antibodies to guselkumab achieved ACR 50 response at Week 24. However, it should be noted that the number of subjects who were positive for antibodies to guselkumab was small (n=5), which limits a definitive conclusion on the impact of antibodies to guselkumab on clinical efficacy.

In study PSA3001, the overall incidence of antibodies to guselkumab was 5.4% (20/367 subjects) through Week 52 and 8.7% (32/367 subjects) through Week 60 (final DBL) in subjects with PsA (Mod5.3.5.1/PSA3001/W60CSR/Tab5 and /AttTIR01A). Through Week 52, the incidence of antibodies to guselkumab was 3.2% (4/126 subjects) in the guselkumab 100 mg q8w group, 7.0% (9/128 subjects) in the guselkumab 100 mg q4w group, and 6.2% (7/113 subjects) in the placebo→100 mg q4w group. Two (10.0%) of the 20 subjects positive for antibodies to guselkumab were positive for neutralizing antibodies (Nabs) to guselkumab through Week 52 (Mod5.3.5.1/PSA3001/W60CSR/AttTIR02). Five (15.6%) of the 32 subjects positive for antibodies to guselkumab were positive for NAbs to guselkumab through Week 60 (Mod5.3.5.1/PSA3001/W60CSR/AttTIR02A).

Efficacy data (observed) with no missing data imputation were used in this analysis. The proportions of subjects who achieved ACR 20 or ACR 50 responses at Week 52 were evaluated by antibodies to guselkumab status through Week 52 for subjects who were treated with guselkumab. For subjects who were positive for antibodies to guselkumab through Week 52, the presence of antibodies to guselkumab did not seem to preclude ACR 20 or ACR 50 responses (Mod5.3.5.1/PSA3001/W60CSR/AttTIRACR01 and /AttTIRACR02, respectively). Among the 13 subjects who were positive for antibodies to guselkumab through Week 52 and had an ACR evaluation at Week 52, 9 subjects achieved ACR 20 response and 4 subjects achieved ACR 50 response at Week 52.

PSA3002

Improvement in Signs and Symptoms of Psoriatic Arthritis

ACR Response

Since the mean change from baseline in the total modified vdH-S score at Week 24 was not significant for the guselkumab 100 mg q8w group (adjusted p=0.068), the key secondary ACR response endpoints for the guselkumab q8w group (ie, ACR 50 and ACR 70 at Week 24 and ACR 20 and ACR 50 at Week 16), which were all placed below the modified vdH-S score test in the graphical procedure *(Assessor's note:*

see Clinical efficacy/Statistical methods/Multiplicity testing subsection of this clinical AR), were not formally tested for the guselkumab 100 mg q8w group and only nominal p-values are presented.

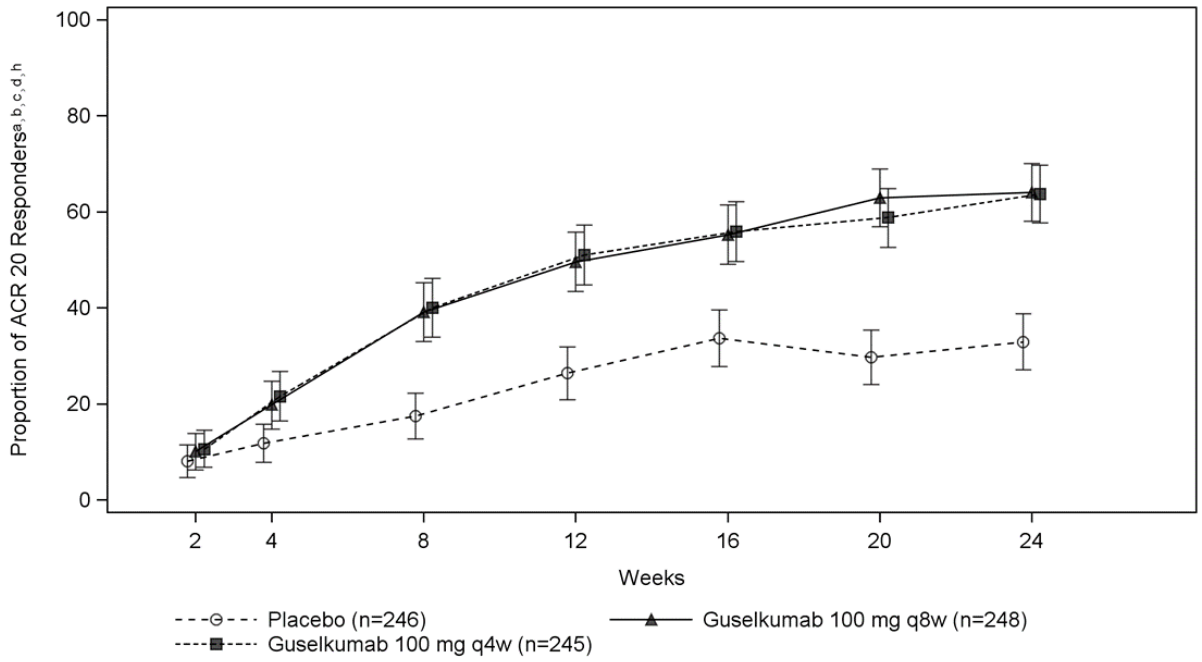
Table 5.4.2.21 : Number of Subjects who Achieved an ACR 20, ACR 50, and ACR 70 Response at Week 24 and Week 16; Full Analysis Set 1 in Study CNTO1959PSA3002

	Placebo	Guselkumab	
		100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
ACR 20 at Week 24			
Subjects in response[a]	81 (32.9%)	159 (64.1%)	156 (63.7%)
Adjusted (nominal) p-value[b]		< 0.001 (< 0.001)	< 0.001 (< 0.001)
ACR 20 at Week 16			
Subjects in response[a]	83 (33.7%)	137 (55.2%)	137 (55.9%)
Adjusted (nominal) p-value[b]		nft[c] (< 0.001)	0.006 (< 0.001)
ACR 50 at Week 24			
Subjects in response[a]	35 (14.2%)	78 (31.5%)	81 (33.1%)
Adjusted (nominal) p-value[b]		nft[c] (< 0.001)	0.006 (< 0.001)
ACR 50 at Week 16			
Subjects in response[a]	23 (9.3%)	71 (28.6%)	51 (20.8%)
Adjusted (nominal) p-value[b]		nft[c] (< 0.001)	0.006 (< 0.001)
ACR 70 at Week 24			
Subjects in response[a]	10 (4.1%)	46 (18.5%)	32 (13.1%)
Adjusted (nominal) p-value[b]		nft[c] (< 0.001)	0.006 (< 0.001)

[a] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[b] The graph-based multiple comparison procedure "gMCP" package in the R software was used to calculate the adjusted p-values based on the multiplicity control testing procedure**.** Nominal p-values are given in parentheses and based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL).
[c] Not formally tested (nft) in the hierarchical testing procedure because a prior endpoint did not achieve statistical significance.

ACR Response Over Time

Figure 5.4.2.6 :Line Plot of the Number of Subjects Achieving ACR 20 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)



Subjects who had not met any TF criteria prior to Week 24 are included in these plots. Subjects with missing data were assumed to be non-responders. The confidence intervals are based on the Wald statistic.

Figure 5.4.2.7 : Line Plot of the Number of Subjects Achieving ACR 50 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)

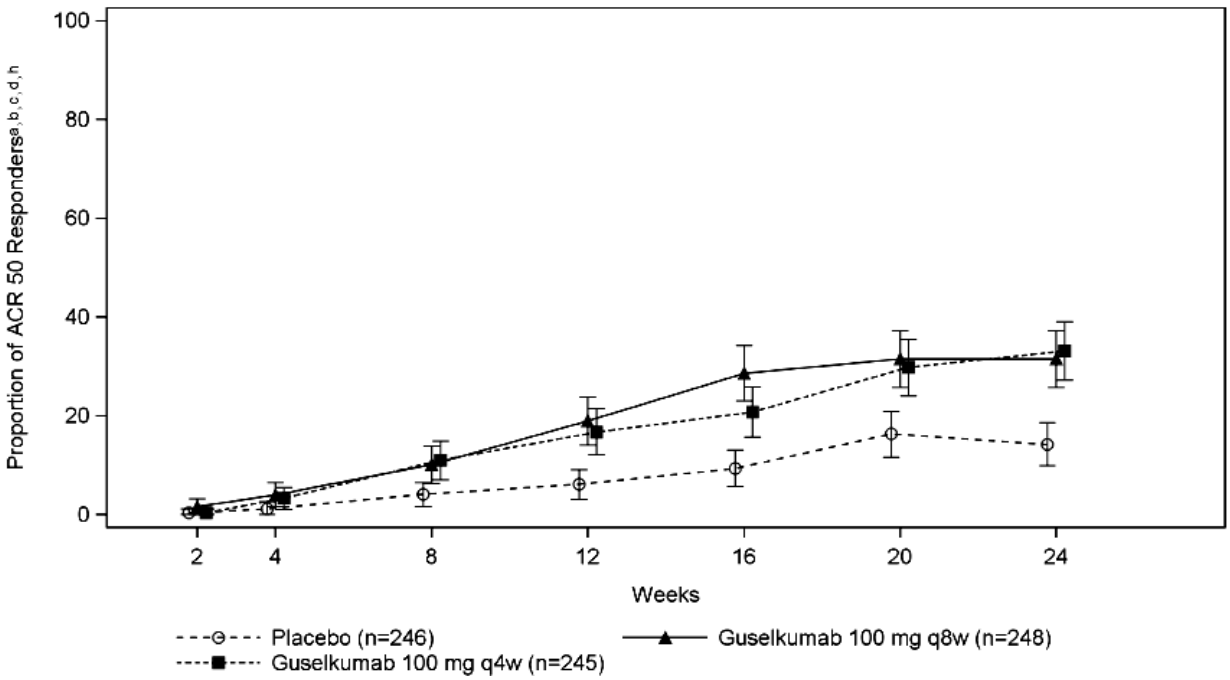
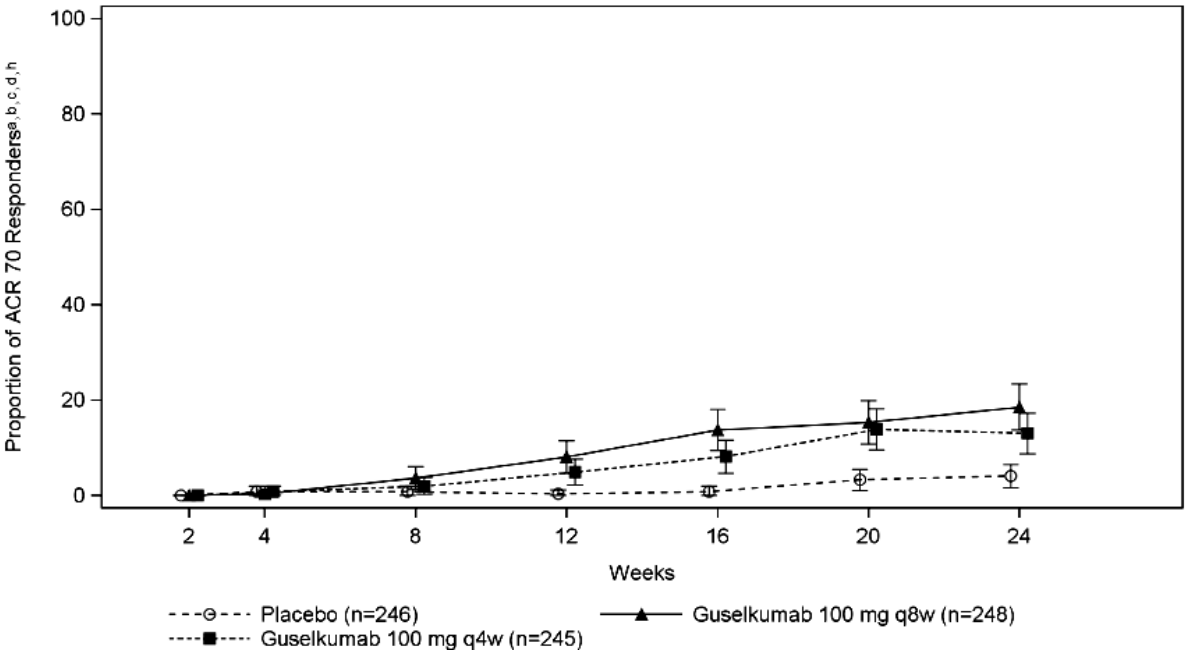


Figure 5.4.2.8 : Line Plot of the Number of Subjects Achieving ACR 70 Response by Visit Through Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)



Combined, these analyses demonstrate the impact of both guselkumab q8w and q4w dose regimens on the signs and symptoms of PsA and show comparable efficacy between the guselkumab q8w and q4w dose regimens.

Subgroup Analyses for ACR20 response

Subgroup analyses were carried out for ACR 20 response at Week 24 over subgroups defined by demography, baseline disease characteristics, and prior and concomitant use of medications for PsA. A consistent treatment benefit was observed for ACR 20 response in each of the two guselkumab dose groups among the subgroups defined by baseline demographics, baseline disease characteristics, and prior and baseline medication use. For the majority of subgroups, the lower bound of the 95% CI of the difference in proportion of ACR 20 responders was above 0 for each guselkumab treatment compared with placebo, in favor of guselkumab.

Table 5.4.2.22 Number of Subjects who achieved ACR 20 response at week 24 for subgroups defined by baseline vdH-S scoreQuartiles, based on the composite estimand, Full Analysis Set 1, Study CNTO1959PsA3002

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Subjects with baseline vdH-S score < 4.0	55	57	63
Subjects evaluable for ACR 20 Response at Week 24[a]	55	57	63
Subjects with ACR 20 Response[b,h]	19 (34.5%)	42 (73.7%)	39 (61.9%)
All subjects (including those with imputed data)	55	57	63
Subjects with ACR 20 Response[b,c,h]	19 (34.5%)	42 (73.7%)	39 (61.9%)
% Difference (95% CI)[d]		41.3 (25.3, 57.3)	26.1 (9.3, 42.9)
p-value[e]		< 0.001	0.005
Subjects with baseline vdH-S score ≥ 4.0 - < 10.5	65	61	65
Subjects evaluable for ACR 20 Response at Week 24[a]	64	61	65
Subjects with ACR 20 Response[b,h]	20 (31.3%)	43 (70.5%)	48 (73.8%)
All subjects (including those with imputed data)	65	61	65
Subjects with ACR 20 Response[b,c,h]	20 (30.8%)	43 (70.5%)	48 (73.8%)
% Difference (95% CI)[d]		37.8 (22.6, 53.1)	43.2 (27.8, 58.6)
p-value[e]		< 0.001	< 0.001
Subjects with baseline vdH-S score ≥ 10.5 - < 26.5	68	70	45
Subjects evaluable for ACR 20 Response at Week 24[a]	68	69	45
Subjects with ACR 20 Response[b,h]	23 (33.8%)	43 (62.3%)	24 (53.3%)
All subjects (including those with imputed data)	68	70	45
Subjects with ACR 20 Response[b,c,h]	23 (33.8%)	43 (61.4%)	24 (53.3%)
% Difference (95% CI)[d]		28.6 (12.7, 44.4)	18.2 (0.7, 35.6)
p-value[e]		< 0.001	0.056
Subjects with baseline vdH-S score ≥ 26.5	58	60	72
Subjects evaluable for ACR 20 Response at Week 24[a]	58	59	72
Subjects with ACR 20 Response[b,h]	19 (32.8%)	31 (52.5%)	45 (62.5%)
All subjects (including those with imputed data)	58	60	72
Subjects with ACR 20 Response[b,c,h]	19 (32.8%)	31 (51.7%)	45 (62.5%)
% Difference (95% CI)[d]		20.6 (3.8, 37.5)	31.0 (15.1, 46.9)
p-value[e]		0.026	< 0.001

[a] Subjects either have an observed ACR 20 response status or met a Treatment Failure (TF) criterion.
[b] Defined as observed responders who had not met any TF criteria prior to Week 24.
[c] Subjects with missing data are assumed to be non-responders.
[d] The confidence intervals are based on the Wald statistic.
[e] The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL).
[h] ACR 20 response is defined as ≥ 20% improvement from baseline in both tender joint count (68 joints) and swollen joint count (66 joints), and ≥ 20% improvement from baseline in at least 3 of the 5 assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, and CRP.
[AH_TEFACRXR01.RTF] [CNTO1959\PSA3002\DBR_WEEK_24\RE_WEEK_24\PROD\AH_TEFACRXR01.SAS] 09AUG2019, 09:19

Sensitivity analysis for ACR20 response (PSA3002)

To test the robustness of the primary endpoint analysis, the following sensitivity and supplementary analyses were performed:

- Tipping point analyses via exhaustive scenario (all nominal p<0.001 for both doses)
- Treatment policy estimand using MI imputed data (both nominal p<0.001).

- Tipping point analyses for the treatment policy estimand (all nominal p<0.001 for both doses).
- Alternative composite estimand (both nominal p<0.001).
- Per-protocol estimand (both nominal p<0.001).

The results from these sensitivity and supplemental analyses including the evaluation of the impact of treatment failure and missing data imputation rules were consistent with the primary analysis, demonstrating the robustness of the primary analysis results.

Disease Activity Index Score 28 Response

At Week 24, a significantly greater reduction in the mean change from baseline in DAS28 (CRP) score was observed in the guselkumab 100 mg q8w group (LSmean: −1.59) and q4w group (LSmean: −1.62) compared with the placebo group (LSmean: −0.97; both adjusted p<0.001).

As early as the first evaluation at Week 2, a greater reduction in DAS28 (CRP) score from baseline was observed in the guselkumab 100 mg q8w and q4w groups compared with the placebo group, which increased by time.

At Week 24, the proportions of subjects achieving a DAS28 (CRP) good or moderate response were 75.4% and 80.0% in the guselkumab q8w and q4w groups, respectively, compared with 52.4% (both nominal p<0.001) in the placebo group.

Greater proportions of subjects with DAS28 (CRP) remission at Week 24 were observed in the guselkumab q8w and q4w groups (24.6% and 23.3%, respectively) compared with the placebo group (8.5%; both nominal p<0.001).

Table5.4.2.23 Number of Subjects Achieving DAS 28 (CRP) Remission by Visit Through Week 24 in Evaluable Subjects Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Subjects evaluable for DAS28 (CRP) remission[a]			
Week 2	242	244	239
Subjects with DAS28 (CRP) remission[b,h]	2 (0.8%)	6 (2.5%)	6 (2.5%)
Week 4	241	243	235
Subjects with DAS28 (CRP) remission[b,h]	5 (2.1%)	13 (5.3%)	12 (5.1%)
Week 8	240	238	241
Subjects with DAS28 (CRP) remission[b,h]	2 (0.8%)	26 (10.9%)	23 (9.5%)
Week 12	241	241	236
Subjects with DAS28 (CRP) remission[b,h]	15 (6.2%)	35 (14.5%)	30 (12.7%)
Week 16	241	239	237
Subjects with DAS28 (CRP) remission[b,h]	17 (7.1%)	46 (19.2%)	42 (17.7%)
Week 20	240	239	234
Subjects with DAS28 (CRP) remission[b,h]	24 (10.0%)	57 (23.8%)	53 (22.6%)
Week 24	240	243	239
Subjects with DAS28 (CRP) remission[b,h]	23 (9.6%)	61 (25.1%)	58 (24.3%)

Dactylitis

Dactylitis Endpoints Analyzed with Data from Study CNTO1959PSA3002 Only

At baseline, overall 44.9% of the subjects in study PSA3002 were diagnosed with dactylitis. Distribution of subjects with dactylitis at baseline was well-balanced over treatment groups. (See Baseline disease characteristics/Study PSA3002 subsection of this clinical AR.)

Greater proportions of subjects who achieved dactylitis resolution were observed in the q8w (56.8%) and q4w (63.6%) groups at Week 24 compared with placebo (38.4%; nominal p=0.007 and p<0.001, respectively). The number of subjects achieving dactylitis resolution was larger in both guselkumab treatment groups compared with the placebo group and was higher for Q4W group than for Q8W group at each visit from Week 2 through Week 24.

Among subjects with dactylitis at baseline, a greater reduction from baseline in dactylitis score at Week 24 was observed in both the guselkumab q8w and q4w groups compared with the placebo group (both nominal p=0.002).

Enthesitis Endpoints Analyzed with Data from Study CNTO1959PSA3002 Only

At baseline, overall 68.6% of the subjects in study PSA3002 were diagnosed with enthesitis.

Greater proportions of subjects who achieved enthesitis resolution were observed in the q8w (53.8%) and q4w groups (43.5%) at Week 24 compared with placebo (30.3%; nominal p<0.001 and p=0.017, respectively). The number of subjects achieving enthesitis resolution was larger in both guselkumab treatment groups compared with the placebo group at each visit from Week 4 through Week 24.

At Week 24, a greater reduction from baseline in LEI score was observed for subjects in both the guselkumab q8w (LSmean: -1.60) and q4w groups (LSmean: -1.52) compared with placebo (LSmean: -1.03; nominal p<0.001 and p=0.002, respectively. A greater reduction from baseline in LEI score was observed in both the guselkumab q8w and q4w groups compared with the placebo group at each visit when enthesitis was assessed through Week 24.

Other Measures of Disease Activity

Table 10: Summary of Results for Disease Activity Measures; Full Analysis Set 1 in Study CNTO1959PSA3002

	Placebo	Guselkumab	
		100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Change from baseline in DAPSA index			
N[a]	243	246	245
LSMean (95% CI)[b]	**-15.849** (**-17.923**, -13.775)	**-24.036** (**-26.102**, **-21.970**)	-25.158 (**-27.234**, -23.082)
p-value[b]		< 0.001	< 0.001
Change from baseline in PASDAS			
N[a]	238	243	239
LSMean (95% CI)[b]	-1.336 (-1.516, -1.156)	-2.403 (**-2.582**, -2.225)	-2.399 (-2.579, -2.219)
p-value[b]		< 0.001	< 0.001
Minimal Disease Activity (MDA)			
N	246	248	245
Subjects with MDA response[c]	15 (6.1%)	62 (25.0%)	46 (18.8%)
p-value[d]		< 0.001	< 0.001
Very Low Disease Activity (VLDA)			
N	246	248	245
Subjects with VLDA response[c]	3 (1.2%)	11 (4.4%)	12 (4.9%)
p-value[d]		0.032	0.018
Change from baseline in GRACE Index			
N[a]	244	245	243
LSMean (95% CI)[b]	**-1.198** (**-1.395**, **-1.001**)	**-2.593** (**-2.789**, **-2.397**)	-2.589 (-2.786, -2.392)
p-value[b]		< 0.001	< 0.001
Change from baseline in mCPDAI			
N[a]	240	243	239
LSMean (95% CI)[b]	-1.30 (-1.57, -1.04)	-2.94 (-3.20, -2.68)	-3.09 (-3.35, -2.83)
p-value[b]		< 0.001	< 0.001
PsARC response			
N	246	248	245
Subjects in response[c]	110 (44.7%)	180 (72.6%)	168 (68.6%)
p-value[d]		< 0.001	< 0.001

[a] Subjects either have an observed change from baseline or response at this visit or met TF criteria prior to this visit.
[b] The LS mean and nominal p-values are based on the MMRM analysis.
[c] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[d] The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL).
DAPSA=Disease Activity Index for Psoriatic Arthritis; GRACE= GRAPPA Composite Score; mCPDAI=modified Composite Psoriatic Disease Activity Index; PASDAS=Psoriatic Arthritis Disease Activity Score; PsARC=Psoriatic Arthritis Responder Criteria;

*Adapted from study PSA3002 tables: TEFDAPSA01.RTF, **14FEB2020, 10:23**; TEFPASDAS01.RTF, **14FEB2020, 10:24**; TEFMDA01.RTF, 09AUG2019, 08:21; TEFVLDA01.RTF, 09AUG2019, 08:30; TEFGRACE01.RTF, **14FEB2020, 10:23**; TEFMCPDAI01.RTF, 09AUG2019, 08:11; TEFPSARC01.RTF, 01APR2019, 16:01;*

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

At baseline, 34.9% (258/739) of all subjects presented with the PsA subset of spondylitis with peripheral arthritis as their primary arthritic presentation as judged by the investigator. Among these subjects, a greater reduction from baseline in BASDAI was observed in both guselkumab groups compared with the

placebo group at each visit at which BASDAI was evaluated (Weeks 8, 16, and 24; all nominal p<0.001, except p=0.007 at Week 8 in the guselkumab q8w group). Change from baseline was similar for the two guselkumab groups at each time points.

For the threshold response of ≥50% improvement from baseline (a prespecified analysis), both studies PSA3001 and PSA3002 showed similar results for the two guselkumab dose regimens.

Improvement in Skin Disease

Investigator's Global Assessment of Psoriasis

In subjects with a ≥3% BSA of psoriatic involvement and an IGA score ≥2 at baseline (n=543), a significantly greater proportion of subjects in both the guselkumab 100 mg q8w and q4w groups (70.5% and 68.5%, respectively) achieved an IGA response of 0 (cleared) or 1 (minimal) and ≥2- grade reduction from baseline in IGA score at Week 24 compared with the placebo group (19.1%; adjusted p<0.001).

Greater proportions of subjects who achieved an IGA score of 0 (cleared) at Week 24 were observed in the guselkumab q8w (50.0%) and q4w (50.5%) groups compared with the placebo group (7.7%, both nominal p<0.001).

Psoriasis Area and Severity Index

Greater proportions of subjects with a PASI 50, 75, 90, and 100 response were observed in the guselkumab 100 mg q8w and q4w groups compared with the placebo group at Week 16 and Week 24 (all nominal p<0.001; Table).

Table 5.4.2.25: Number of Subjects who Achieved a PASI 50, PASI 75, PASI 90, and PASI 100 Response at Week 24; Full Analysis Set 1, Subjects with ≥3% Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score ≥2 (Mild) at Baseline in Study CNTO1959PSA3002

	Placebo	Guselkumab	
		100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1[a]	183	176	184
PASI 50			
Subjects in response[b]	69 (37.7%)	163 (92.6%)	166 (90.2%)
p-value[c]		< 0.001	< 0.001
PASI 75			
Subjects in response[b]	42 (23.0%)	139 (79.0%)	144 (78.3%)
p-value[c]		< 0.001	< 0.001
PASI 90			
Subjects in response[b]	18 (9.8%)	121 (68.8%)	112 (60.9%)
p-value[c]		< 0.001	< 0.001
PASI 100			
Subjects in response[b]	5 (2.7%)	80 (45.5%)	82 (44.6%)
p-value[c]		< 0.001	< 0.001

[a] Includes only subjects who had ≥3% BSA of psoriatic involvement and an IGA score ≥2 (mild) at baseline in the Full analysis Set 1.
[b] Defined as all responders who had not met any TF criteria prior to Week 24. Subjects with missing data are assumed to be non-responders.
[c] The p-values (nominal) are based on the CMH test, stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL).

Subjects Achieving Both PASI 75 and ACR 20 Responses

Table 5.4.2.26 Number of Subjects Achieving Both PASI 75 and ACR 20 Responses by Visit Through Week 24, Based on the Composite Estimand; Full Analysis Set 1 Among the Subjects

with **≥3%** Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score **≥2** (mild) at Baseline (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects Who had ≥3% Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score ≥2 (mild) at Baseline	183	176	184
Week 16			
Subjects evaluable for PASI 75 and ACR 20 responses[a]	181	175	181
Subjects with PASI 75 and ACR 20 responses[b,h]	19 (10.5%)	86 (49.1%)	89 (49.2%)
All subjects (including those with imputed data)	183	176	184
Subjects with PASI 75 and ACR 20 responses[b,c,h]	19 (10.4%)	86 (48.9%)	89 (48.4%)
% Difference (95% CI)[d]		38.4 (29.9, 46.9)	37.7 (29.4, 46.1)
p-value[e]		< 0.001	< 0.001
Week 24			
Subjects evaluable for PASI 75 and ACR 20 responses[a]	182	175	183
Subjects with PASI 75 and ACR 20 responses[b,h]	21 (11.5%)	100 (57.1%)	105 (57.4%)
All subjects (including those with imputed data)	183	176	184
Subjects with PASI 75 and ACR 20 responses[b,c,h]	21 (11.5%)	100 (56.8%)	105 (57.1%)
% Difference (95% CI)[d]		45.1 (36.5, 53.6)	45.8 (37.4, 54.2)
p-value[e]		< 0.001	< 0.001

Improvement in Physical Function

Physical function was assessed using the HAQ-DI questionnaire. The population in this study had moderate to severe disability as indicated by the median baseline HAQ-DI score of 1.250 across all treatment groups.

Table 5.4-2.27 Summary of the Change from Baseline in HAQ-DI Score at Week 24 Based on the Composite Estimand Using MI and an ANCOVA Model; Full Analysis Set 1 (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Change from baseline in HAQ-DI[a,b]			
Subjects evaluable[b]			
N	244	246	245
Mean (SD)	-0.1527 (0.51258)	-0.3892 (0.53778)	-0.4097 (0.50084)
Median	-0.1250	-0.2500	-0.3750
Range	(-2.250; 1.375)	(-2.250; 1.125)	(-2.000; 1.000)
IQ range	(-0.3750; 0.1250)	(-0.6250; 0.0000)	(-0.7500; 0.0000)
All subjects (including those with imputed data)[a,c,b]			
N	246	248	245
Mean (SE)[d]	-0.1557 (0.03280)	-0.3891 (0.03407)	-0.4097 (0.03200)
Model Based Estimates of the Mean Change[a,c,b]			
LSMean (95% CI)[e]	-0.1300 (-0.1912, -0.0687)	-0.3672 (-0.4282, -0.3062)	-0.4004 (-0.4617, -0.3390)
LSMean difference (95% CI)		-0.2372 (-0.3210, -0.1534)	-0.2704 (-0.3544, -0.1864)
p-value[f]		< 0.001	< 0.001

[a]Defined as the change from baseline using observed data or 0 (no improvement) if a subject met Treatment Failure (TF)
criteria prior to Week 24.
[b]Subjects either have an observed change from baseline at this visit or met TF criteria prior to this visit.
[c]Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[d]The average of the mean, taken over all the MI data sets, is presented. The variance of the mean is the weighted sum of the average within-imputation variance and the between-imputation variance.

At Week 24, the proportion of subjects achieving a clinically meaningful HAQ-DI response (defined as ≥0.35 improvement in HAQ-DI from baseline) was 50.0%, and 56.1% in the guselkumab q8w and q4w groups compared with the placebo group (31.4%, both nominal p<0.001).

Impact on Structural Damage

Change From Baseline in Total Modified vdH-S Score at Week 24

At baseline, the median erosion, joint space narrowing (JSN), and vdH-S scores for hands and feet were generally similar across the treatment groups; however, the median total modified vdH-S and erosion scores were slightly higher in the guselkumab 100 mg q8w group (11.50 and 5.50, respectively) compared with the guselkumab q4w group (10.00 and 4.62, respectively) and the placebo group (10.50 and 4.36, respectively).

At Week 24, the mean change from baseline in total modified vdH-S score was significantly smaller (less progression of structural damage) in the guselkumab 100 mg q4w group and numerically smaller in the guselkumab q8w group compared with the placebo group (adjusted p=0.006 and p=0.068, respectively)

Table 5.4.2.28: Summary of the Change from Baseline in the Modified vdH-S score at Week 24 Based on the Treatment Policy Estimand, Using MI and an ANCOVA Model (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 for Structural Damage	246	248	245

Table 5.4.2.28: Summary of the Change from Baseline in the Modified vdH-S score at Week 24 Based on the Treatment Policy Estimand, Using MI and an ANCOVA Model (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Change from baseline in modified vdH-S score			
LSMean (95% CI)[a]	0.95 (0.61, 1.29)	0.52 (0.18, 0.86)	0.29 (-0.05, 0.63)
LSMean difference (95% CI)		-0.43 (-0.90, 0.03)	-0.66 (-1.13, -0.19)
Adjusted p-value[b]		0.068	0.006
Nominal p-value[b]		0.068	0.006

[a] Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI). The LSmean for each MI data set is calculated based on an ANCOVA model for the change from baseline at Week 24. The combined LSmean which is the average of the LSmean taken over all the MI data sets, is presented.

[b] The graph based multiple comparison procedure "gMCP" package in the R software was used to calculate the adjusted p-values based on the multiplicity control testing procedure. The nominal p-values are based on the approximately normal distribution of the combined LSmean.

Adapted from PSA3002 study: TEFXRAY01.RTF, 09AUG2019, 08:30; **Error! Reference source not found.**

Sensitivity Analyses

To test the robustness of the major secondary endpoint analysis for change from baseline in modified vdH-S score at Week 24, sensitivity analyses were performed. In each of these analyses at Week 24, a numerically smaller change from baseline (less progression) was observed in both guselkumab treatment groups compared with the placebo group. These analyses also confirmed the robustness of the finding of a smaller change from baseline in vdH-S (less radiographic progression) for the guselkumab 100 mg q4w group compared with the placebo group.

Other Radiographic Endpoints at Week 24

TEFXRAY12: Number of Subjects with a Change of ≤ 0 from Baseline in the Modified vdH-S Scores Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 for Structural Damage	246	248	245
Subjects evaluable for change from baseline in the modified vdH-S score at Week 24[a]	245	247	240
Subjects with change of ≤0 from baseline in the modified vdH-S score[b,h]	159 (64.9%)	157 (63.6%)	164 (68.3%)
All subjects including those with imputed data	246	248	245
Average proportion of responders[b,c,d,h]	64.7	**63.5**	67.3
% Difference (95% CI)[e]		-1.3 (**-9.7**, 7.1)	2.6 (-5.8, 10.9)
p-value[f]		**0.752**	**0.558**

TEFXRAY12: Number of Subjects with a Change of ≤ 0 from Baseline in the Modified vdH-S Scores Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w

[a] Subjects have an observed change from baseline in the modified vdH-S score.
[b] Subjects with an observed change from baseline of <=0 in the modified vdH-S score regardless of Treatment Failure (TF).
[c] Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[d] The average, over the MI data sets, of the proportion of responders are presented.
[e] The confidence intervals are based on the combined Wald statistic using CMH weights for each imputation.
[f] The p-value is based on the combined standardized Wilson-Hilferty transformation of the CMH test statistic (stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL)) from each imputation.
[h] The modified vdH-S score is the sum of the erosion score (hand, feet) and joint space narrowing (JSN) score (hand, feet). The joint erosion score is the total erosion severity in 40 joints of the two hands and 12 joints of the 2 feet, for a maximum erosion score of 320. Each joint is scored from 0 – 5 with 0 indicating no erosion, and 5 indicating complete collapse of the bone. The JSN score is the total JSN score in the same 52 joints as above. Each joint is scored from 0 – 4 with 0 indicating no JSN, and 4 indicating an absence of joint space, for a maximum JSN score of 208. The maximum modified vdH-S score is 528.

[TEFXRAY12.RTF] [CNTO1959\PSA3002\DBR_WEEK_24\RE_WEEK_24\PROD\TEFXRAY12.SAS] 14FEB2020, 10:51

TEFXRAY13: Number of Subjects with a Change of ≤ 0 from Baseline in the Modified vdH-S Erosion Scores Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 for Structural Damage	246	248	245
Subjects evaluable for change from baseline in the modified vdH-S erosion score at Week 24[a]	245	247	240
Subjects with change of ≤0 from baseline in the modified vdH-S erosion score[b,h]	164 (66.9%)	164 (66.4%)	174 (72.5%)
All subjects including those with imputed data	246	248	245
Average proportion of responders[b,c,d,h]	66.8	66.3	71.4
% Difference (95% CI)[e]		-0.5 (-8.8, 7.7)	4.6 (-3.5, 12.8)
p-value[f]		0.867	0.268

TEFXRAY14: Number of Subjects with a Change of ≤ 0 from Baseline in the Modified vdH-S Joint Space Narrowing Scores at Week 24, Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 for Structural Damage	246	248	245
Subjects evaluable for change from baseline in the modified vdH-S JSN score at Week 24[a]	245	247	240
Subjects with change of ≤0 from baseline in the modified vdH-S JSN score[b,h]	193 (78.8%)	195 (78.9%)	195 (81.3%)
All subjects including those with imputed data	246	248	245
Average proportion of responders[b,c,d,h]	78.6	78.8	80.2
% Difference (95% CI)[e]		0.2 (-6.9, 7.3)	1.6 (-5.6, 8.7)
p-value[f]		0.903	0.669

[a] Subjects have an observed change from baseline in the modified vdH-S joint space narrowing score.
[b] Subjects with an observed change from baseline of <=0 in the modified vdH-S joint space narrowing score regardless of Treatment Failure (TF).
[c] Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[d] The average, over the MI data sets, of the proportion of responders are presented.
[e] The confidence intervals are based on the combined Wald statistic using CMH weights for each imputation.
[f] The p-value is based on the combined standardized Wilson-Hilferty transformation of the CMH test statistic (stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL)) from each imputation.
[h] The JSN score is the total JSN score in 40 joints of the two hands and 12 joints of the 2 feet. Each joint is scored from 0 – 4 with 0 indicating no JSN, and 4 indicating an absence of joint space, for a maximum JSN score of 208.

[TEFXRAY14.RTF] [C:\NTO1959\PSA3002\DRR_WEEK_24\RF_WEEK_24\PROD\TEFXRAY14.SAS] 09AUG2019 08:54

TEFXRAY15: Number of Subjects with a Change of ≤ 0.5 from Baseline in the Modified vdH-S Scores at Week 24, Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 for Structural Damage	246	248	245
Subjects evaluable for change from baseline in the modified vdH-S score at Week 24[a]	245	247	240
Subjects with change of ≤0.5 from baseline in the modified vdH-S score[b,h]	177 (72.2%)	184 (74.5%)	190 (79.2%)
All subjects including those with imputed data	246	248	245
Average proportion of responders[b,c,d,h]	72.1	74.4	**78.0**
% Difference (95% CI)[e]		2.2 (-5.5, 9.9)	**5.9** (-1.6, 13.5)
p-value[f]		0.577	**0.125**

TEFXRAY15: Number of Subjects with a Change of ≤ 0.5 from Baseline in the Modified vdH-S Scores at Week 24, Based on the Treatment Policy Estimand and MI (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w

[a] Subjects have an observed change from baseline in the modified vdH-S score.
[b] Subjects with an observed change from baseline of <=0.5 in the modified vdH-S score regardless of Treatment Failure (TF).
[c] Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[d] The average, over the MI data sets, of the proportion of responders are presented.
[e] The confidence intervals are based on the combined Wald statistic using CMH weights for each imputation.
[f] The p-value is based on the combined standardized Wilson-Hilferty transformation of the CMH test statistic (stratified by baseline use of non-biologic DMARD (yes, no) and CRP prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL)) from each imputation.
[h] The modified vdH-S score is the sum of the erosion score (hand, feet) and joint space narrowing (JSN) score (hand, feet). The joint erosion score is the total erosion severity in 40 joints of the two hands and 12 joints of the 2 feet, for a maximum erosion score of 320. Each joint is scored from 0 – 5 with 0 indicating no erosion, and 5 indicating complete collapse of the bone. The JSN score is the total JSN score in the same 52 joints as above. Each joint is scored from 0 – 4 with 0 indicating no JSN, and 4 indicating an absence of joint space, for a maximum JSN score of 208. The maximum modified vdH-S score is 528.

[TEFXRAY15.RTF] [CNTO1959\PSA3002\DBR_WEEK_24\RE_WEEK_24\PROD\TEFXRAY15.SAS] 19FEB2020, 12:51

A smaller change from baseline (less radiographic progression) in modified vdH-S erosion score at Week 24 was observed in the guselkumab q4w group (LSmean: 0.13) compared with the placebo group (LSmean: 0.58; nominal p=0.010). A numerically smaller change from baseline was observed in the guselkumab q8w group (LSmean change: 0.36; nominal p=0.199) compared with the placebo group. A smaller change from baseline (less radiographic progression) in modified vdH-S JSN score was observed in both the guselkumab q8w and q4w groups (both LSmean: 0.16) compared with the placebo group (LSmean: 0.37; nominal p=0.028 and p=0.031, respectively.

The proportions of subjects who had no progression of structural damage at Week 24, analyzed as subjects who had either a change from baseline in total modified vdH-S score of ≤0 or ≤0.5 or the SDC showed:

- The proportions of subjects with a change of ⩽0 from baseline in modified vdH-S scores were 63.5% and 67.3% in the guselkumab q8w and q4w groups compared with 64.7% in the placebo group (nominal p=0.752 and p=0.558, respectively.
- The proportions of subjects with a change of ⩽0.5 from baseline in modified vdH-S scores were 74.4% and 78.0% in the guselkumab q8w and q4w groups compared with 72.1% in the placebo group (nominal p=0.577 and p=0.125, respectively.
- At Week 24, the proportions of subjects without radiographic progression based on the SDC were consistent with those reported above.

The separations between the guselkumab groups and the placebo group are more distinct both above SDC and below -SDC.

There are 3 outliers with change from baseline >15: 2 in placebo group and 1 in the guselkumab 100 mg q8w group. There is 1 outlier with change from baseline <−10 in the guselkumab 100 mg q4w group.

Structural Damage Benefit at Week 52: Read Campaign 2 Results

For the q4w dose regimen, the mean change in total modified vdH-S score in Period 2 (0.62) was similar to that observed in Period 1 (0.46), as were the mean changes in erosion (0.39 and 0.31, respectively) and JSN (0.23 and 0.15, respectively) scores.

In the q8w group, a smaller mean change in total modified vdH-S score was observed in Period 2, from Week 24 to Week 52, (0.23) compared with Period 1, from baseline to Week 24, (0.73). This finding of a smaller mean change in total vdH S score in Period 2 compared with Period 1 was also observed in the erosion score (0.10 and 0.57, respectively), while a similar mean change was noted in the JSN score across the 2 periods (0.16 and 0.13, respectively). These data indicate that the effect of the guselkumab q8w dose regimen on inhibition of radiographic progression appears to increase beyond Week 24.

Table 8: Summary of the Changes in the Modified vdH-S Score, Joint Space Narrowing (JSN) Score, and Erosion Score by Period, Based on Observed Data (Read Campaign 2); Full Analysis Set 2 for Structural Damage (Study CNTO1959PSA3002)

	From Baseline to Week 24 (Period 1)	From Week 24 to Week 52 (Period 2)
Analysis set: Full Analysis Set 2 for Structural Damage		
Guselkumab 100 mg q4w (N=234)		
Subjects evaluable for change in modified vdH-S score[b]		
N	232	229
Mean (SD)	0.46 (2.457)	0.62 (2.530)
Median	0.00	0.00
Range	(-11.0; 14.5)	(-4.5; 19.5)
IQ range	(-0.50; 0.75)	(-0.50; 0.50)
Subjects evaluable for change in JSN score[b]		
N	232	229
Mean (SD)	0.15 (0.968)	0.23 (1.088)
Median	0.00	0.00
Range	(-4.5; 7.5)	(-4.0; 8.5)
IQ range	(0.00; 0.00)	(0.00; 0.00)
Subjects evaluable for change in erosion score[b]		
N	232	229
Mean (SD)	0.31 (1.881)	0.39 (1.725)
Median	0.00	0.00
Range	(-10.0; 12.0)	(-4.0; 12.5)
IQ range	(-0.50; 0.50)	(-0.50; 0.50)
Placebo → Guselkumab 100 mg q4w[a] (N=238)		
Subjects evaluable for change in modified vdH-S score[b]		
N	231	230
Mean (SD)	1.00 (3.193)	0.25 (1.635)
Median	0.00	0.00
Range	(-5.0; 28.0)	(-6.5; 9.8)
IQ range	(0.00; 1.00)	(0.00; 0.50)
Subjects evaluable for change in JSN score[b]		
N	231	230
Mean (SD)	0.25 (1.135)	0.07 (0.635)
Median	0.00	0.00
Range	(-2.1; 10.0)	(-3.5; 4.1)
IQ range	(0.00; 0.00)	(0.00; 0.00)
Subjects evaluable for change in erosion score[b]		
N	231	230
Mean (SD)	0.75 (2.310)	0.17 (1.277)
Median	0.00	0.00
Range	(-4.5; 18.0)	(-4.5; 7.5)
IQ range	(0.00; 1.00)	(0.00; 0.50)

[a] Placebo randomized subjects are scheduled to crossover to guselkumab 100 mg q4w from Week 24 onwards.
[b] Evaluable subjects have observed change for the specified period.

Adapted from: PsA/Mod5.3.5.1/PSA3002/W52CSR/Tab19

Table 9:	Change From Baseline in Modified vdH-S Score for Subjects in the Guselkumab 100 mg q8w Group; Read Campaign 2	
	From Baseline to Week 24 (Period 1)	From Week 24 to Week 52 (Period 2)
Analysis set: Full Analysis Set 2 for Structural Damage		
Guselkumab 100 mg q8w (N=240)		
Subjects evaluable for change in modified vdH-S score[b]		
N	238	235
Mean (SD)	0.73 (2.504)	0.23 (1.808)
Median	0.00	0.00
Range	(-9.5; 20.0)	(-5.5; 12.0)
IQ range	(0.00; 1.00)	(-0.50; 0.50)
Subjects evaluable for change in JSN score[b]		
N	238	235
Mean (SD)	0.16 (0.780)	0.13 (0.705)
Median	0.00	0.00
Range	(-2.5; 7.0)	(-1.5; 6.0)
IQ range	(0.00; 0.00)	(0.00; 0.00)
Subjects evaluable for change in erosion score[b]		
N	238	235
Mean (SD)	0.57 (2.035)	0.10 (1.422)
Median	0.00	0.00
Range	(-7.0; 13.0)	(-5.5; 8.5)
IQ range	(0.00; 1.00)	(-0.50; 0.50)

[a] Placebo randomized subjects are scheduled to crossover to guselkumab 100 mg q4w from Week 24 onwards.
[b] Evaluable subjects have observed change for the specified period.
Adapted from: PsA/Mod5.3.5.1/PSA3002/W52CSR/Tab19

Improvement in Health-related Quality of Life

36-Item Short Form Health Survey

At Week 24, a significantly greater improvement from baseline in the SF-36 PCS and SF-36 MCS scores was demonstrated in the guselkumab 100 mg q4w group compared with the placebo group (adjusted p=0.006 for both).

A numerically greater improvement from baseline in the SF-36 PCS and MCS scores at Week 24 was observed for the guselkumab 100 mg q8w group compared with the placebo group (nominal p<0.001). Since the mean change from baseline in total modified vdH-S score at Week 24 was not significant for the guselkumab 100 mg q8w group, the change from baseline in the SF-36 PCS score at Week 24 was not formally tested for the guselkumab q8w group. SF-36 PCS and MCS scores were larger in the guselkumab q8w group compared with the guselkumab q4w group at each visit.

At Week 24, the proportions of subjects who achieved ≥5-point improvement from baseline in SF-36 PCS score were 60.1% and 55.9% in the guselkumab q8w and q4w groups, respectively, compared with 40.2% in the placebo group.

At Week 24, the proportion of subjects who achieved ≥5-point improvement from baseline in SF-36 MCS score was 37.5% and 34.3% in the guselkumab q8w and q4w groups, respectively, compared with 30.9% in the placebo group.

Functional Assessment of Chronic Illness Therapy – Fatigue

A greater increase from baseline (improvement) in FACIT-Fatigue scores was observed in both guselkumab groups compared with the placebo group at each visit the FACIT-Fatigue was evaluated (Weeks 8, 16, and 24; all nominal p<0.001). The scores in the guselkumab q8w were comparable with the q4w group at Week 24.

Similarly, the percentage of subjects with clinically meaningful improvement (≥4 points) from baseline in FACIT-Fatigue at Week 24 was observed to be greater in the guselkumab q8w (60.5%) and q4w (59.6%) groups compared with the placebo group (45.5%; nominal p<0.001 and p=0.002, respectively).

Efficacy and Pharmacokinetics

Exposure-Response analyses are discussed in details in the PK/PD modelling subsection of this AR.

Efficacy and Immunogenicity

The incidence of antibodies to guselkumab across all guselkumab treatment groups through Week 24 was 2.0%. The limited number of subjects positive for antibodies to guselkumab precludes a definitive conclusion regarding the impact of antibodies to guselkumab on efficacy.

In study PSA3002, the overall incidence of antibodies to guselkumab was 4.0%, (29/727 subjects) through Week 52 in subjects with PsA. Through Week 52, the incidence of antibodies to guselkumab was 5.7% (14/247 subjects) in the guselkumab 100 mg q8w group, 3.3% (8/243 subjects) in the guselkumab 100 mg q4w group, and 3.0% (7/237 subjects) in the placebo→100 mg q4w group. Three (10.3%) of the 29 subjects with positive antibodies to guselkumab status were positive for NAbs to guselkumab.

The proportions of subjects who achieved ACR 20 or ACR 50 responses at Week 52 were evaluated by antibodies to guselkumab status through Week 52 for subjects who were treated with guselkumab. For subjects who were positive for antibodies to guselkumab through Week 52, the presence of antibodies to guselkumab did not seem to preclude ACR 20 or ACR 50 responses. Among the 20 subjects who were positive for antibodies to guselkumab through Week 52 and had an ACR evaluation at Week 52, 15 subjects achieved ACR 20 response and 11 subjects achieved ACR 50 response at Week 52.

Ancillary analyses

Risk Factor Analysis for Structural Damage Progression

In long-term cohort studies of PsA patients, it has been estimated that approximately 50% to 60% of patients with PsA will not exhibit structural damage progression over time. In study PSA3002, 35.1% (86 of 245) of subjects in the placebo group exhibited structural damage progression, defined as a >0 change from baseline in modified vdH-S score, at Week 24. Since many patients with PsA do not experience structural joint damage, and the q8w and q4w dose regimens appear to have similar benefit in signs and symptoms, additional analyses were performed to examine which patients may derive additional benefit from the q4w dose regimen in terms of inhibition of structural damage progression and risk factors were identified that may predict the risk for structural damage progression.

Risk Factor Identification

Two CART analyses of radiographic progression were conducted to assess the predictive capability of eight risk factors.

The first CART analysis was conducted using historical data from placebo-treated subjects from 5 clinical studies in PsA conducted by the Applicant to identify predictive factors in a population with active PsA. This analysis identified the number of joints with erosion at baseline as the risk factor with highest predictive value for identifying subjects at greater risk for progression of structural damage.

The second CART analysis, which excluded the 2 radiographic based risk factors (number of joints with erosion and number of joints with JSN), identified baseline CRP level as the risk factor with

highest predictive value for identifying subjects at greater risk for progression of structural damage. These final CART analyses identified (i) **≤5** versus >5 joints with erosions and (ii) CRP **≤1.4** versus >1.4 as the cutoffs that identified patients at low risk.

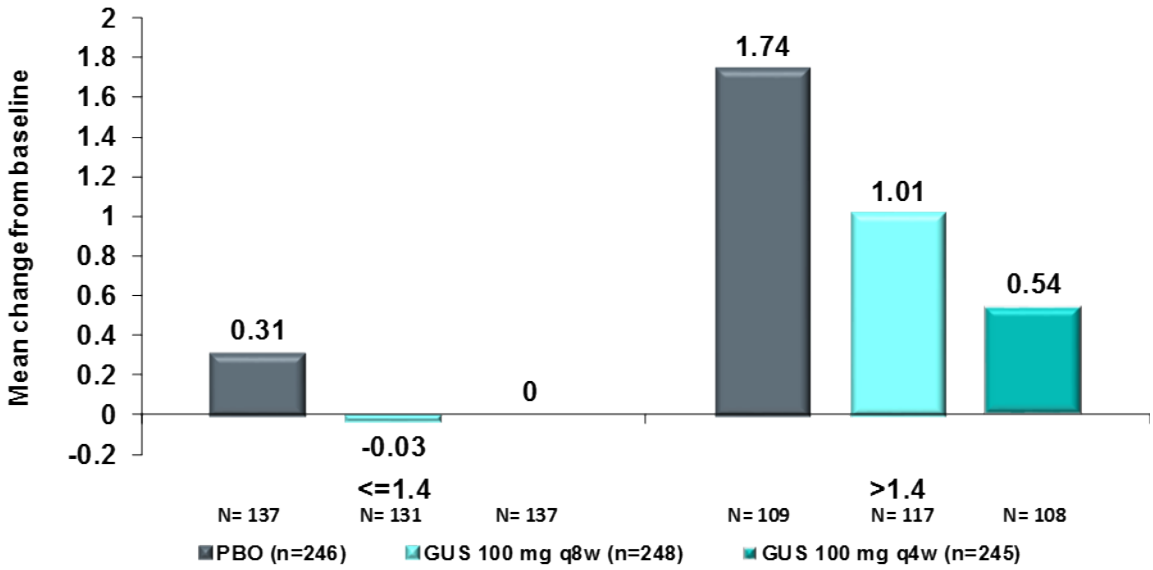
Next, the 2 independently identified risk factors were evaluated for predictive potential in PSA3002 study. Results obtained in the analyses of radiographic data from placebo-treated subjects in study PSA3002 using the risk factors identified above were comparable to those observed for the historical placebo data analyses from prior PsA clinical studies.

CRP Risk Factor

CRP effectively discriminated high and low erosion risk subjects in the placebo group; Figure . 5.4.2.9

In the placebo group, subjects with a CRP level ≤1.4 mg/dL (n=137) showed change from baseline in the total modified vdH-S score at Week 24 of LSmean change 0.31, while subjects with CRP >1.4 mg/dL (n=109) showed a change from baseline in the total modified vdH-S score at Week 24 of LSmean change 1.74; Figure 10; Appendix AH_TEFXRAY01_CRP). These observations suggest that CRP provides good discriminatory value in identifying patients at low versus high risk of structural damage progression.

Figure 5.4.2.9: Mean Change from Baseline in Modified vdH-S Score at Week 24 by Baseline CRP Level (mg/dL); Subjects Randomized in Study CNTO1959PSA3002



Additional analyses were conducted to evaluate radiographic outcomes by treatment group in subjects at low versus high risk of structural damage progression based on baseline CRP level. No difference was observed between the guselkumab q8w and q4w dose regimens, suggesting that in this population, the guselkumab q4w dose regimen does not add incremental benefit over the q8w regimen.

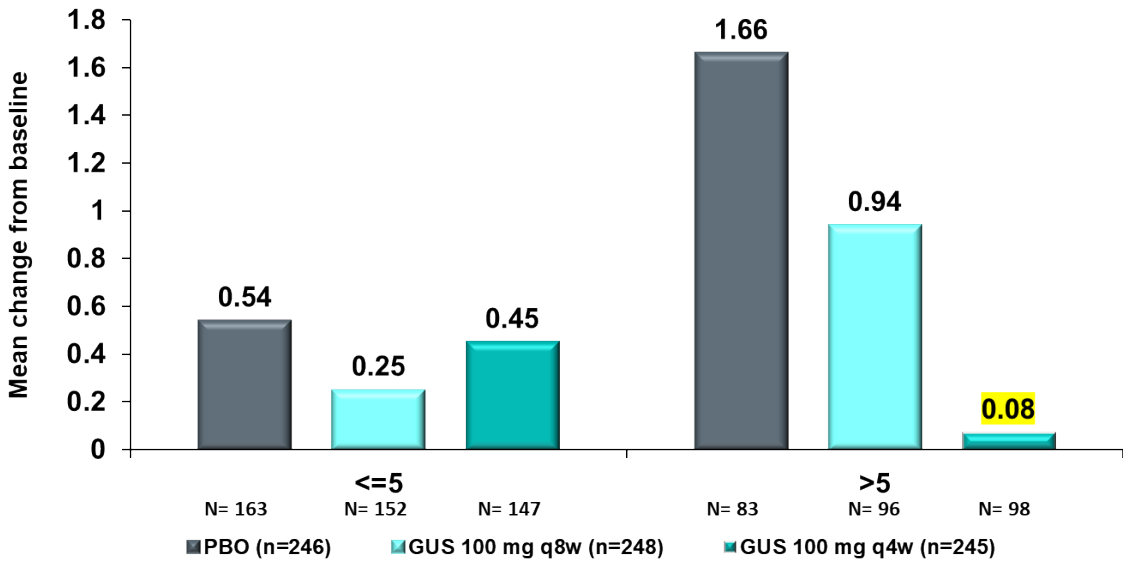
In contrast, for subjects at high risk (ie, CRP >1.4 mg/dL), subjects in the guselkumab 100 mg q4w group (n=108) had less progression as reflected by the change from baseline in the total modified vdH-S score at Week 24 of 0.54 compared with 1.01 for subjects in the guselkumab 100 mg q8w group (n=117) and 1.74 for subjects in the placebo group (n=109).

Erosion Risk Factor

Subjects with **≤5** joints with erosions (n=163) had an LSmean change of 0.54 from baseline in the total modified vdH-S score at Week 24, while subjects with >5 joints with erosions (n=83) had an LSmean change of 1.66 from baseline in the total modified vdH-S score at Week 24 (Figure 5.4.2.10.). For subjects with ≤5 joints with erosions, a comparable effect was observed for both the guselkumab q4w (LSmean change: 0.45) and q8w (LSmean change: 0.25) dose regimens:

In contrast, for subjects at high risk (ie, >5 joints with erosions), those in the guselkumab 100 mg q4w group (n=98) had less progression as reflected by the change from baseline in the total modified vdH-S score at Week 24 (LSmean change: 0.08) compared with subjects in the guselkumab q8w group (n=96, LSmean change: 0.94) and the placebo group (n=83, LSmean change: 1.66; Figure 11 and Appendix AH_TEFXRAY01_VECNT). These observations show that the q4w dose regimen has greater impact on structural damage progression than the guselkumab q8w regimen in this subpopulation.

Figure 11: Mean Change from Baseline in Modified vdH-S Score at Week 24 by Baseline Number of Joints with Erosion; Subjects Randomized in Study CNTO1959PSA3002

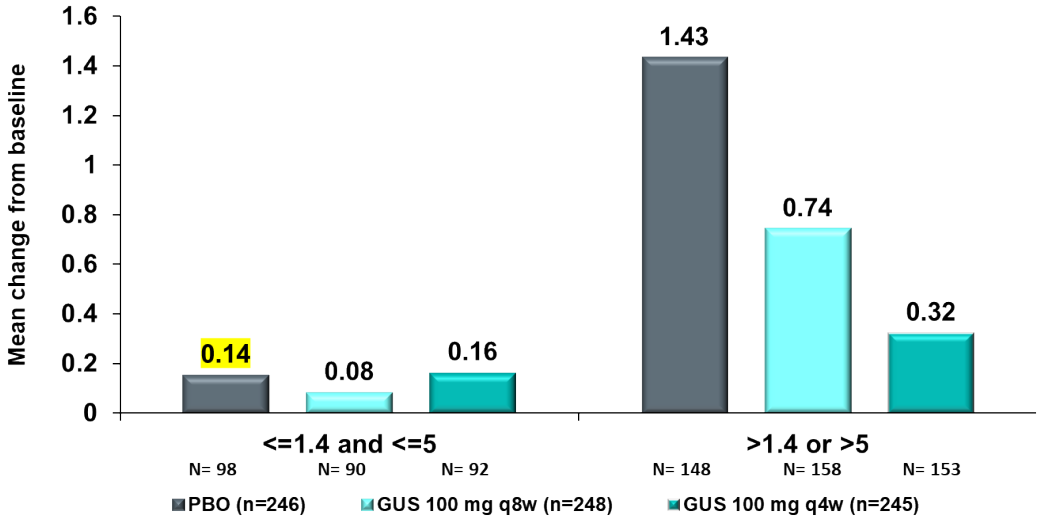


*Adapted from: AH_TEFXRAY01_VECNT.RTF, **19FEB2020**, **15:43***

Regardless of whether a single risk factor or a combination of both risk factors were used, the same pattern emerged with: (1) higher structural damage progression for subjects receiving placebo in the high-risk group when compared to those in the low-risk group, (2) a similar effect for the guselkumab q8w and q4w dose regimens within the low-risk group, and (3) greater inhibition of progression of q4w compared to q8w within the high-risk group. Further, the least restrictive versus most restrictive definitions of low-risk subjects (ie, subjects who had either CRP ≤1.4 mg/dL or ≤5 joints with erosions, which represented almost 80% of subjects versus subjects who had both CRP ≤1.4 mg/dL and ≤5 joints with erosions, which represented approximately 40% of patients) performed equally well in identifying a subpopulation who had a minimal risk of structural damage progression and who did equally well with guselkumab q8w or q4w dose regimens. Thus, many patients may be sufficiently treated with the q8w regimen and would not require q4w dosing for structural damage benefit.

CRP or Erosion Risk Factor

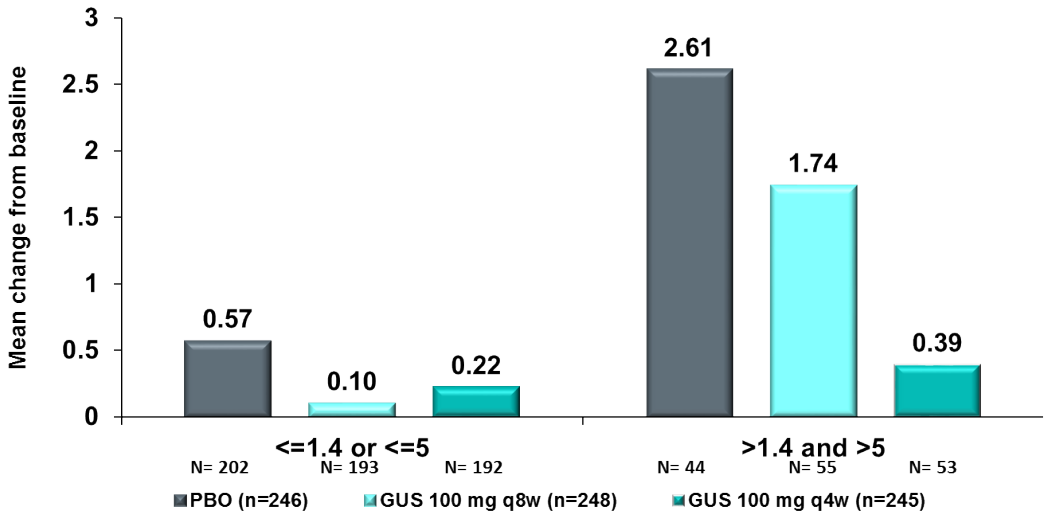
Figure 12: Mean Change from Baseline in Modified vdH-S Score at Week 24 by Baseline CRP Level (mg/dL) OR Number of Joints with Erosion; Subjects Randomized in Study CNTO1959PSA3002



*Adapted from: AH_TEFXRAY01_CRPVECNT.RTF, **19FEB2020, 15:36***

CRP and Erosion risk factor

Figure 3: Mean Change from Baseline in Modified vdH-S Score at Week 24 by Baseline CRP Level (mg/dL) AND Number of Joints with Erosion; Subjects Randomized in Study CNTO1959PSA3002



Adapted from: AH_TEFXRAY01_CRPVECNT.RTF, 22AUG2019, 07:57

Further Characterization and Justification of Subjects at High Risk of Structural Damage Progression who are Appropriate for q4w Dosing

Consistent with the European Medicines Agency (EMA) Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013),4 factors that define subgroups of the target

population were considered at the planning stage of the PsA Phase 3 program, with particular focus on factors for which there are reasons to believe that they are prognostic for radiographic outcomes based on prior evidence and/or biological plausibility.

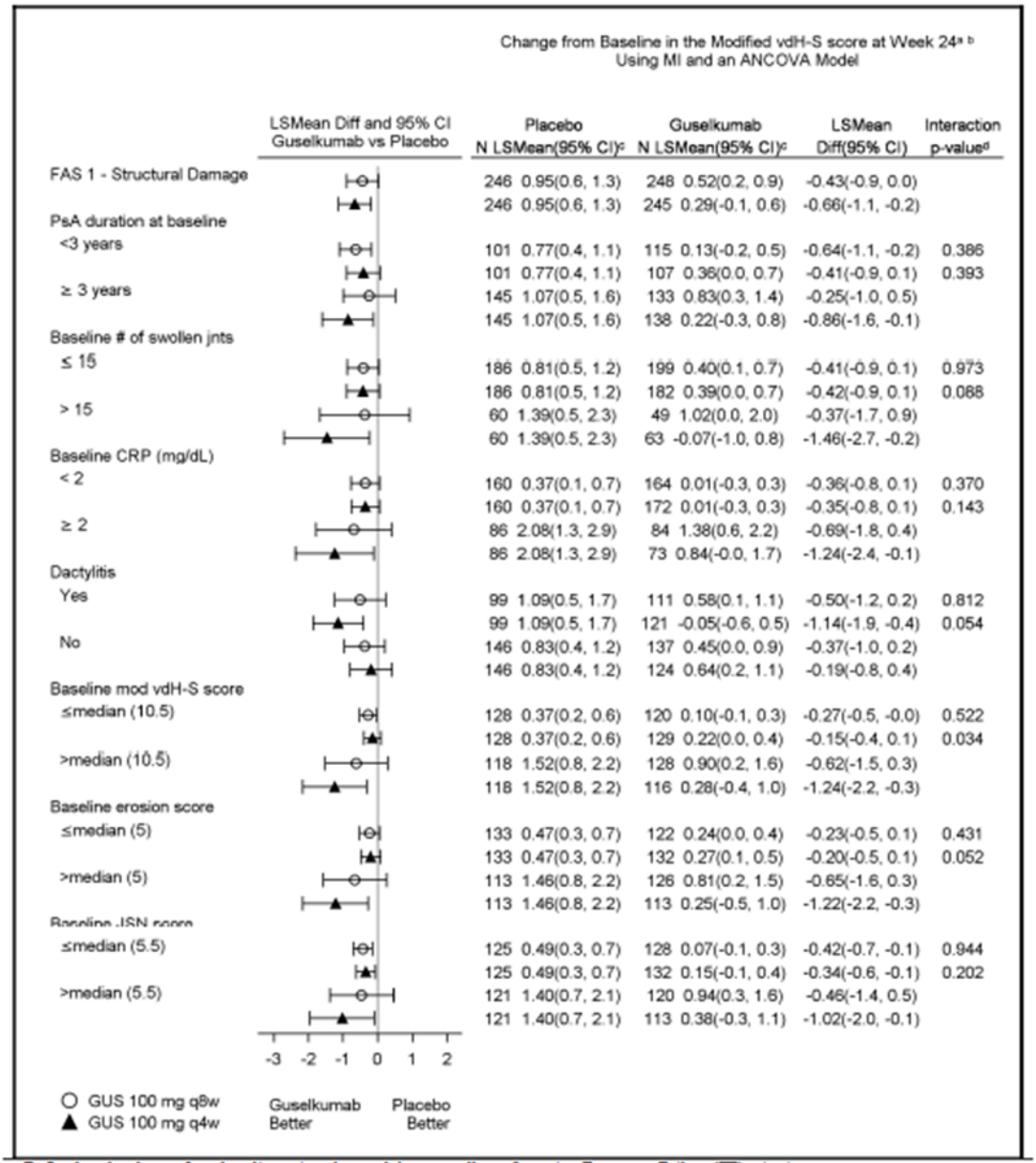
As C-reactive protein (CRP) is a well-known predictor for radiographic progression, it was selected as a stratification factor in PSA3002 to ensure that subjects with high CRP were balanced across the treatment groups to minimize potential bias in evaluation of radiographic endpoints. Further, prespecified subgroup analyses included baseline demographics, baseline disease characteristics, and prior baseline medication use where relevant baseline disease characteristics which predict risk for radiographic progression in PsA were also included, i.e.:

- PsA disease duration (<1, >1 ≤3, or >3 years);
- CRP (<1, 1 to <2, ≥ 2 mg/dL and by tertile);
- number of swollen joint counts (<10, 10 to 15, or >15); and
- presence or absence of dactylitis.

For the endpoint of mean change from baseline in total modified vdH-S score at Week 24, there was an apparent dose-response in the following 4 subgroups defined at baseline (hereafter referred as the ‘ clinical risk factors’): PsA disease duration >3 years, CRP ≥2 mg/dL, number of swollen joint counts >15, or presence of dactylitis. These data are summarized in Figure 3 with the corresponding reciprocal subgroups pooled for clarity (hereafter referred to as ‘complementary subgroup’).

Additional post-hoc analyses were conducted in subgroups with baseline total modified vdH-S score, erosion score or joint space narrowing score ≤ versus > than the median of the overall study population. A dose-response was also observed in subgroups with > median baseline radiographic scores, but not in the subgroups with ≤ median baseline radiographic scores, suggesting that the protective effect of the q4w regimen is particularly relevant for patients with higher baseline total modified vdH-S, erosion, and joint space narrowing scores (Figure 3)

Figure 3: **LSMean Difference and 95% Confidence Interval for Comparing Change from Baseline in the Modified vdH-S score at Week 24 in the Guselkumab Groups Versus the Placebo Group for Subgroups Defined by Baseline Disease Characteristics (Read Campaign 1); Full Analysis Set 1 for Structural Damage (Study CNTO1959PSA3002)**



[a] Defined as the change from baseline using observed data regardless of meeting Treatment Failure (TF) criteria.
[b] Missing data is assumed to be Missing at Random (MAR) and is imputed using Multiple Imputation (MI).
[c] The LSmean for each MI data set is calculated based on an Analysis of Covariance (ANCOVA) model for the change from baseline at Week 24. The combined LSmean which is the average of the LSmean, taken over all the MI data sets, is presented.
[d] The interaction p-values are from an ANCOVA model based on the observed data.

[EMA_GEFXRAYSG01.RTF] [CNTO1959\Z_ADHOC_REQ\DBR_PSA_SBLA\RE_EMA_20191223\PROD\EMA_GEFXRAYSG01.SAS] 28FEB2020, 12:50

Summary of main study(ies)

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 Efficacy for trial PSA3001

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis including those Previously Treated with Biologic **Anti-TNFα** Agent(s)			
Study identifier	CNTO1959PSA3001		
Design	Phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study		
	1. Duration of main phase: 2. Duration of Extension phase:		1. placebo-controlled 24 weeks 2. active treatment period from week 24-week 52 safety follow-up 8 weeks after week 52
Hypothesis	Superiority		
Treatments groups	placebo		s.c. placebo q4w from Week 0 to Week 20, and crossover at Week 24 to receive guselkumab 100 mg q4w through Week 48; N=
	guselkumab q4w		s.c. guselkumab 100 mg every 4 weeks (q4w) from Week 0 through Week 48; N=
	guslekumab q8w		s.c. guselkumab 100 mg at Weeks 0 and 4, then q8w (Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48) to maintain the blind; N=
Endpoints and definitions	Primary endpoint	ACR20	proportion of subjects who achieve an ACR 20 response at Week 24
	secondary endpoint	ACR50	Proportion of subjects who achieve an ACR 50 response at Week 24
	secondary endpoint	DAS28	Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 24
	secondary endpoint	dactilitis	Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline.
	secondary endpoint	enthesitis	Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline
	secondary endpoint	PASI90	Proportions of subjects who achieve ⩾75%, ⩾ 90%, and 100% improvement in Psoriatic Area and Severity Index (PASI) score from baseline by visit over time through Week 24 among subjects with ⩾3% BSA psoriatic involvement and an IGA score of ⩾2 (mild) at baseline
	secondary endpoint	HAQ-DI	Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24
Database lock	Weeks 24 and End of Study (Week 60). date of data cutoff: 14.03. 2019.		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	ITT week 24		

Descriptive statistics and estimate variability	Treatment group	placebo	100 mg q8w guselkumab	100 mg q4w guselkumab
	Number of subject	126	127	128
	primary endpoint ACR20 N (%)	28 (22.2%)	66 (52.0%)	76 (59.4%)
	ACR50 N (%)	11 (8.7%)	38 (29.9%)	46 (35.9%)
	DAS28 LSmean (95% CI)	-0.70 (-0.89, -0.51)	-1.43 (-1.61, -1.24)	-1.61 (-1.80, -1.42)
	dactilitis N , resolution(%)	27 (49.1%)	32 (65.3%)	24 (63.2%)
	enthesitis N, resolution (%)	21 (27.3%)	29 (40.3%)	35 (47.9%)
	PASI90 N (%)	9 (11.5%)	41 (50.0%)	56 (62.9%)
	HAQ-DI LSmean (95% CI)	-0.0743 (-0.1605, 0.0119	-0.3225 (-0.4082, -0.2369)	-0.3968 (-0.4825, -0.3112)

Effect estimate per comparison all parameters at week 24	Primary endpoint ACR20	Comparison groups	placebo vs. guselkumab q8w
		% difference	29.8%
		95% CI	18.6; 41.1
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		proportion of subject who achieved 20% response	37.1%
		% difference	26.1; 48.2
		95% CI	<0.001
	ACR50	Comparison groups	placebo vs. guselkumab q8w
		% difference	21.4%
		95% CI	12.1; 30.7
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		% difference	27.2%
		95% CI	17.6; 36.8
		P-value	<0.001
	DAS28	Comparison groups	placebo vs. guselkumab q8w
		difference in LSmean	-0.73

		95% CI	-1.61; -1.24
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		difference in LSmean	-0.91
		95% CI	-1.16; -0.66
		P-value	<0.001
	dactilitis	Comparison groups	placebo vs. guselkumab q8w
		% difference	16.6%
		95% CI	-1.5; 34.8
		P-value	0.088
		Comparison groups	placebo vs. guselkumab q4w
		% difference	13.4%
		95% CI	-6.9; 33.7
		P-value	0.212
	enthesitis	Comparison groups	placebo vs. guselkumab q8w
		% difference	13%
		95% CI	-1.6; 27.5
		P-value	0.094
		Comparison groups	placebo vs. guselkumab q4w
		% difference	19.8%
		95% CI	4.9; 34.6
		P-value	p=0.013
	PASI90	Comparison groups	placebo vs. guselkumab q8w
		% difference	38.6%
		95% CI	25.8; 51.5
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		% difference	51.7%
		95% CI	39.7; 63.7
		P-value	<0.001
	HAQ-DI	Comparison groups	placebo vs. guselkumab q8w
		difference in LSmeans	-0.2483
		95% CI	-0.3640; -0.1325
		P-value	<0.001

		Comparison groups	placebo vs. guselkumab q4w
		difference in LSmeans	-0.3226
		95% CI	-0.4385; -0.2066
		P-value	<0.001
Notes	-		

Summary of Efficacy for trial PSA3002

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis			
Study identifier	CNTO1959PSA3002		
Design	Phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study		
	3. Duration of main phase: 4. Duration of Extension phase:		3. placebo-controlled 24 weeks 4. active treatment period from week 24-week 52 safety follow-up 8 weeks after week 52
Hypothesis	Superiority		
Treatments groups	placebo		s.c. placebo q4w from Week 0 to Week 20, and crossover at Week 24 to receive guselkumab 100 mg q4w through Week 48; N=
	guselkumab q4w		s.c. guselkumab 100 mg every 4 weeks (q4w) from Week 0 through Week 48; N=
	guslekumab q8w		s.c. guselkumab 100 mg at Weeks 0 and 4, then q8w (Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48) to maintain the blind; N=
Endpoints and definitions	Primary endpoint	ACR20	proportion of subjects who achieve an ACR 20 response at Week 24
	secondary endpoint	ACR50	Proportion of subjects who achieve an ACR 50 response at Week 24
	secondary endpoint	DAS28	Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 24
	secondary endpoint	dactilitis	Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline.
	secondary endpoint	enthesitis	Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline
	secondary endpoint	PASI90	Proportions of subjects who achieve ⩾75%, ⩾ 90%, and 100% improvement in Psoriatic Area and Severity Index (PASI) score from baseline by visit over time through Week 24 among subjects with ⩾3% BSA psoriatic involvement and an IGA score of ⩾2 (mild) at baseline

	secondary endpoint	HAQ-DI	Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24
Database lock	Weeks 24, 52, and End of Study (Week 112). date of data cutoff: 06 March 2019.		

Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	ITT week 24			
Descriptive statistics and estimate variability	Treatment group	placebo	100 mg q8w guselkumab	100 mg q4w guselkumab
	Number of subject	246	248	245
	primary endpoint ACR20 N (%)	81 (32.9%)	159 (64.1%)	156 (63.7%)
	ACR50 N (%)	35 (14.2%)	78 (31.5%)	81 (33.1%)
	DAS28 LSmean (95% CI)	-0.97 (-1.11, -0.51)	-1.59 (-1.72, -1.45)	-1.62 (-1.76, -1.49)
	dactilitis N , resolution(%)	38 (38.4%)	63 (56.8%)	77 (63.6%)
	enthesitis N, resolution (%)	54 (30.3%)	85 (53.8%)	74 (43.5%)
	PASI90 N (%)	9 (11.5%)	41 (50.0%)	56 (62.9%)
	HAQ-DI LSmean (95% CI)	-0.13 (-0.1912, -0.0687	-0.3672 (-0.4282, -0.3062)	-0.4004 (-0.4617, -0.3390)

Effect estimate per comparison all parameters at week 24	Primary endpoint ACR20	Comparison groups	placebo vs. guselkumab q8w
		% difference	31.2%
		95% CI	22.2; 39.5
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		proportion of subject who achieved 20% response	30.8%
		% difference	22.4; 39.1
		95% CI	<0.001
	ACR50	Comparison groups	placebo vs. guselkumab q8w
		% difference	17.2%

		95% CI	10.0; 24.4
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		% difference	18.8%
		95% CI	11.5; 26.1
		P-value	<0.001
	DAS28	Comparison groups	placebo vs. guselkumab q8w
		difference in LSmean	-0.61
		95% CI	-0.80; -0.43
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		difference in LSmean	-0.65
		95% CI	-0.83; -0.47
		P-value	<0.001
	dactilitis	Comparison groups	placebo vs. guselkumab q8w
		% difference	18.7%
		95% CI	5.7; 31.7
		P-value	0.007
		Comparison groups	placebo vs. guselkumab q4w
		% difference	24.5%
		95% CI	11.8; 37.1
		P-value	<0.001
	enthesitis	Comparison groups	placebo vs. guselkumab q8w
		% difference	23.3%
		95% CI	13.1; 33.5
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		% difference	12.3%
		95% CI	2.6; 22.1
		P-value	p=0.017
	PASI90	Comparison groups	placebo vs. guselkumab q8w
		% difference	58.6%
		95% CI	50.6; 66.6
		P-value	<0.001

		Comparison groups	placebo vs. guselkumab q4w
		% difference	51.3%
		95% CI	43.2; 59.3
		P-value	<0.001
	HAQ-DI	Comparison groups	placebo vs. guselkumab q8w
		difference in LSmeans	-0.2372
		95% CI	-0.3210; -0.1534
		P-value	<0.001
		Comparison groups	placebo vs. guselkumab q4w
		difference in LSmeans	-0.2704
		95% CI	-0.3544; -0.1864
		P-value	<0.001
Notes	-		

Analysis performed across trials (pooled analyses and meta-analysis)

Cross-study comparisons of efficacy focused on comparing results from the two Phase 3 studies, and evaluating consistency in the overall population for:

- The magnitude of treatment effect versus placebo.
- Dose-response in efficacy, focusing on the primary, major secondary and selected other endpoints.
- Time to onset of efficacy and response over time.

The pooled analyses of efficacy data across the 2 Phase 3 studies were performed to provide more precise estimates for treatment differences between each individual guselkumab dose group and the placebo group, and between the 2 guselkumab dose groups at each visit over time to support efficacy assessment and dose selection.

Comparison of Efficacy Results for the Phase 3 Psoriatic Arthritis Studies (at week 24)

Table 5.4.2.29 : Comparison of Individual Study and Pooled Efficacy Results Across Studies as Measured by Primary and Major/Key Secondary Endpoints; Full Analysis Set 1 in Studies CNTO1959PSA3001 and CNTO1959PSA3002

	CNTO1959PSA3001			CNTO1959PSA3002			Pooled data from PSA3001 and PSA3002		
		Guselkumab 100 mg			Guselkumab 100 mg			Guselkumab 100 mg	
	Placebo	q8w	q4w	Placebo	q8w	q4w	Placebo	q8w	q4w
Full Analysis Set 1	126	127	128	246	248	245	372	375	373
ACR 20									
Subjects in response at Week 24 [a]	28	66	76	81	159	156	109	225	232
(Primary endpoint)	(22.2%)	(52.0%)	(59.4%)	(32.9%)	(64.1%)	(63.7%)	(29.3%)	(60.0%)	(62.2%)
Adjusted p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		-	-
Nominal p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001

Table 5.4.2.29 : Comparison of Individual Study and Pooled Efficacy Results Across Studies as Measured by Primary and Major/Key Secondary Endpoints; Full Analysis Set 1 in Studies CNTO1959PSA3001 and CNTO1959PSA3002

	CNTO1959PSA3001			CNTO1959PSA3002			Pooled data from PSA3001 and PSA3002		
		Guselkumab 100 mg			Guselkumab 100 mg			Guselkumab 100 mg	
	Placebo	q8w	q4w	Placebo	q8w	q4w	Placebo	q8w	q4w
Subjects in response at Week 16 [a]	32 (25.4%)	66 (52.0%)	77 (60.2%)	83 (33.7%)	137 (55.2%)	137 (55.9%)	115 (30.9%)	203 (54.1%)	214 (57.4%)
Adjusted p-value [b]		< 0.001	< 0.001		nft [l]	0.006		-	-
Nominal p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
ACR 50									
Subjects in response at Week 24 [a]	11 (8.7%)	38 (29.9%)	46 (35.9%)	35 (14.2%)	78 (31.5%)	81 (33.1%)	46 (12.4%)	116 (30.9%)	127 (34.0%)
Adjusted p-value [b]		< 0.001	< 0.001		nft [l]	0.006		-	-
Nominal p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Subjects in response at Week 16 [a]	16 (12.7%)	29 (22.8%)	34 (26.6%)	23 (9.3%)	71 (28.6%)	51 (20.8%)	39 (10.5%)	100 (26.7%)	85 (22.8%)
Adjusted p-value [b]		0.086	0.006		nft [l]	0.006		-	-
Nominal p-value [b]		0.036	0.006		< 0.001	< 0.001		< 0.001	< 0.001
ACR 70									
Subjects in response at Week 24 [a]	7 (5.6%)	15 (11.8%)	26 (20.3%)	10 (4.1%)	46 (18.5%)	32 (13.1%)	17 (4.6%)	61 (16.3%)	58 (15.5%)
Adjusted p-value [b]		0.086	< 0.001		nft [l]	0.006		-	-
Nominal p-value [b]		0.069	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Psoriasis IGA response at Week 24 [c]									
N	78	82	89	183	176	184	261	258	273
Subjects with IGA response [a]	12 (15.4%)	47 (57.3%)	67 (75.3%)	35 (19.1%)	124 (70.5%)	126 (68.5%)	47 (18.0%)	171 (66.3%)	193 (70.7%)
Adjusted p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		-	-
Nominal p-value [b]		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Change from baseline in HAQ-DI at Week 24 [d]									
LSMean (95% CI) [e]	-0.0743 (-0.1605, 0.0119	-0.3225 (-0.4082, -0.2369)	-0.3968 (-0.4825, -0.3112)	-0.1300 (-0.1912, -0.0687)	-0.3672 (-0.4282, -0.3062)	-0.4004 (-0.4617, -0.3390)	-0.1037 (-0.1554, -0.0519)	-0.3441 (-0.3957, -0.2926)	-0.3927 (-0.4443, -0.3410)
Adjusted p-value [f]		< 0.001	< 0.001		< 0.001	< 0.001		-	-
Nominal p-value [f]		< 0.001	< 0.001		< 0.001	< 0.001		<0.001	<0.001
Change from baseline in DAS28 (CRP) at Week 24 [d]									
LSMean (95% CI) [e]	-0.70 (-0.89, -0.51)	-1.43 (-1.61, -1.24)	-1.61 (-1.80, -1.42)	-0.97 (-1.11, -0.84)	-1.59 (-1.72, -1.45)	-1.62 (-1.76, -1.49)	-0.87 (-0.99, -0.76)	-1.52 (-1.64, -1.41)	-1.61 (-1.72, -1.50)
Adjusted p-value [f]		< 0.001	< 0.001		< 0.001	< 0.001		-	-
Nominal p-value [f]		< 0.001	< 0.001		< 0.001	< 0.001		<0.001	<0.001
Dactylitis at Week 24 [g]									
N	55	49	38	99	111	121	154	160	159
Subjects with resolution of dactylitis [a,h]	27 (49.1%)	32 (65.3%)	24 (63.2%)	38 (38.4%)	63 (56.8%)	77 (63.6%)	65 (42.2%)	95 (59.4%) [i]	101 (63.5%) [i]
Adjusted p-value [b]		-	-		-	-		nft [l]	0.006
Nominal p-value [b]		0.088	0.212		0.007	< 0.001		0.001	< 0.001
Change from baseline in dactylitis score, [d] LSMean (95% CI) [e]	-4.30 (-5.96, -2.63)	-6.11 (-7.81, -4.41)	-5.82 (-7.82, -3.83)	-4.03 (-4.96, -3.10)	-5.95 (-6.83, -5.08)	-5.88 (-6.74, -5.01)	-4.21 (-5.05, -3.36)	-6.10 (-6.92, -5.27)	-5.97 (-6.84, -5.11)
Nominal p-value [f]		0.121	0.225		0.002	0.002		< 0.001	0.002
Enthesitis (LEI) at Week 24 [j]									
N	77	72	73	178	158	170	255	230	243
Subjects with resolution of enthesitis [a,k]	21 (27.3%)	29 (40.3%)	35 (47.9%)	54 (30.3%)	85 (53.8%)	74 (43.5%)	75 (29.4%)	114 (49.6%) [i]	109 (44.9%) [i]
Adjusted p-value [b]		-	-		-	-		nft [l]	0.006
Nominal p-value [b]		0.094	0.013		< 0.001	0.017		< 0.001	< 0.001

Table 5.4.2.29 : Comparison of Individual Study and Pooled Efficacy Results Across Studies as Measured by Primary and Major/Key Secondary Endpoints; Full Analysis Set 1 in Studies CNTO1959PSA3001 and CNTO1959PSA3002

	CNTO1959PSA3001			CNTO1959PSA3002			Pooled data from PSA3001 and PSA3002		
		Guselkumab 100 mg			Guselkumab 100 mg			Guselkumab 100 mg	
	Placebo	q8w	q4w	Placebo	q8w	q4w	Placebo	q8w	q4w
Change from baseline in enthesitis score, [d]	-1.01	-1.35	-1.75	-1.03	-1.60	-1.52	-1.02	-1.52	-1.59
LSMean (95% CI) [e]	(-1.37, -0.66)	(-1.72, -0.98)	(-2.13, -1.38)	(-1.25, -0.81)	(-1.84, -1.37)	(-1.75, -1.29)	(-1.21, -0.82)	(-1.73, -1.31)	(-1.79, -1.38)
Nominal p-value [f]		0.185	0.004		< 0.001	0.002		< 0.001	< 0.001
Change from baseline in SF-36 PCS at Week 24 [d]									
LSMean (95% CI) [e]	1.96 (0.69, 3.24)	6.10 (4.83, 7.37)	6.87 (5.60, 8.14)	3.42 (2.53, 4.32)	7.39 (6.50, 8.29)	7.04 (6.14, 7.94)	2.80 (2.04, 3.56)	6.82 (6.06, 7.58)	6.86 (6.10, 7.62)
Adjusted p-value [f]		< 0.001	< 0.001		nft [l]	0.006		-	-
Nominal p-value [f]		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Change from baseline in SF-36 MCS at Week 24[d]									
LSMean (95% CI)[e]	2.37 (0.93, 3.81)	3.20 (1.78, 4.63)	3.60 (2.17, 5.02)	2.14 (1.07, 3.22)	4.17 (3.10, 5.23)	4.22 (3.14, 5.29)	2.12 (1.23, 3.02)	3.75 (2.86, 4.64)	3.93 (3.03, 4.82)
Adjusted p-value [f]		-	-		nft [l]	0.006		-	-
Nominal p-value [f]		0.398	0.214		0.007	0.006		0.006	0.003
Change from baseline in FACIT-Fatigue at Week 24 [d]									
LSMean (95% CI) [m]	2.206 (0.773, 3.638)	5.609 (4.181, 7.036)	5.841 (4.416, 7.267)	3.559 (2.500, 0.619)	7.550 (6.496, 0.603)	7.111 (6.051, 8.171)	-	-	-
Nominal p-value [m]		< 0.001	< 0.001		< 0.001	< 0.001	-	-	-

a: Defined as all responders who had not met any treatment failure (TF) criteria prior to the specified visit. Subjects with missing data at the given visit are assumed to be non-responders.
b: The adjusted p-value was obtained using the global multiplicity control procedure (PSA/W24/Mod2.7.3/Att3 [PSA3001], PSA/W24/Mod2.7.3/Att4 [PSA3002]). The nominal p-value is based on the CMH test.
c: Defined as a psoriasis IGA response of 0 (cleared) or 1 (minimal) and ≥2-grade reduction from baseline in the IGA psoriasis score at Week 24 in subjects with ≥3% BSA psoriatic involvement and an IGA score ≥2 (mild) at baseline.
d: Defined as the change from baseline using observed data or 0 (no improvement) if a subject met treatment failure (TF) criteria prior to Week 24.
e: Missing data is assumed to be missing at random (MAR) and is imputed using multiple imputation (MI). The LS mean is based on the combined results of the analysis of on covariance (ANCOVA) models over all of the MI data sets.
f: The adjusted p-value was obtained using the global multiplicity control procedure (PSA/W24/Mod2.7.3/Att3 [PSA3001] ,PSA/W24/Mod2.7.3/Att4 [PSA3002]). The nominal p-value is based on the approximately normal distribution of the combined LSmean.
g: Subjects with dactylitis at baseline.
h: Subjects with resolution of dactylitis (dactylitis score >0 at baseline and a dactylitis score of 0 at the analysis visit).
i: Analysis based on the pooled data from PSA3001 and PSA3002 were included in the multiplicity control procedure in PSA3002 and reported in the PSA3002 CSR.
j: Subjects with enthesitis at baseline.
k: Subjects with resolution of enthesitis are those who had a LEI enthesitis score >0 at baseline and an LEI of 0 at the analysis visit.
l: Not formally tested (nft) in the hierarchical testing procedure because a prior endpoint did not achieve statistical significance.
m: The LS mean and p-value are based on the mixed effect model repeated measures (MMRM) analysis.

For the guselkumab q4w group, all multiplicity-controlled endpoints demonstrated statistical significance in both studies PSA3001 and PSA3002. For the guselkumab q8w group in PSA3001, all multiplicity-controlled endpoints except ACR 50 response at Week 16 and ACR 70 response at Week 24 were statistically significant. There were also an apparent modest dose-response relationship between the

two guselkumab groups at ACR20 responder rate and DAS28 remission rate endpoints over time. Note that all ACR components showed numerically better mean baseline values for Q4W group.

For the guselkumab q8w group in PSA3002, due to the fact that the mean change from baseline in total modified vdH-S score was not statistically significant, subsequent endpoints including ACR 20 and ACR 50 responses at Week 16, ACR 50 and ACR 70 responses at Week 24, change from baseline in SF-36 PCS at Week 24, change from baseline in SF-36 MCS at Week 24, and resolution of dactylitis and resolution of enthesitis at Week 24 were not formally tested and nominal p-values are presented even if most of these response rate data are close to or even higher than those for guselkumab Q4W outcomes in PSA3002 study.

Dactylitis Endpoints Analyzed with Pooled Data from Studies CNTO1959PSA3001 and CNTO1959PSA3002

In both Phase 3 studies, numerically greater proportions of subjects in the guselkumab q8w and q4w groups achieved resolution of dactylitis at Week 24 compared with placebo . In the pooled analyses, a significantly greater proportion of subjects in the guselkumab q4w group and a numerically greater proportion of subjects in the guselkumab q8w group achieved resolution of dactylitis compared with placebo. The treatment effects were comparable for between the guselkumab q8w and q4w groups (18.0% and 21.3%, respectively).

Numerically greater decreases (improvement) from baseline in dactylitis scores at Week 24 were observed for both the guselkumab q8w and q4w groups compared with placebo for both Phase 3 studies. In the pooled analyses, the treatment effects were comparable for the guselkumab q8w and q4w groups compared with placebo (LSmean difference: -1.89 and -1.77, respectively).

Enthesitis Endpoints Analyzed with Pooled Data from Studies CNTO1959PSA3001 and CNTO1959PSA3002

In both Phase 3 studies, numerically greater proportions of subjects in the guselkumab q8w and q4w groups achieved resolution of enthesitis at Week 24 compared with placebo. In the pooled analyses, a significantly greater proportion of subjects in the guselkumab q4w group and a numerically greater proportion of subjects in the guselkumab q8w group achieved resolution of enthesitis compared with placebo. The treatment effect was numerically larger in the q8w group (20.1%) compared with the q4w group (14.6%). However, since the mean change from baseline in the total modified vdH-S score at Week 24 was not significant for the guselkumab 100 mg q8w group, the proportion of subjects achieving enthesitis resolution at Week 24 in the q8w group was not formally compared with the placebo group.

Numerically greater decreases (improvement) from baseline in enthesitis scores at Week 24 were observed for both the guselkumab q8w and q4w groups compared with placebo for both Phase 3 studies. In the pooled analyses, a significantly greater proportion of subjects in the guselkumab q4w group and a numerically greater proportion of subjects in the q8w group achieved enthesitis resolution at Week 24 compared with placebo. In the pooled analyses, the treatment effects were comparable for the guselkumab q8w and q4w groups compared with placebo (LSmean difference: -0.50 and -0.57, respectively).

Among subjects with enthesitis at baseline, a greater reduction from baseline in LEI score at Week 24 was observed in both the guselkumab 100 mg q8w (LSmean: −1.52) and q4w (LSmean: −1.59) groups compared with the placebo group (LSmean: −1.02; both nominal $p<0.001$) based on pooled data from PSA3001 and PSA3002.

Other Efficacy Endpoints Related to BASDAI

Only subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA completed the BASDAI. Subjects with spondylitis and peripheral arthritis at baseline included 86, 73, and

99 subjects in the guselkumab 100 mg q4w, guselkumab 100 mg q8w, and placebo. Subjects with spondylitis and peripheral arthritis at baseline and BASDAI score >0 at baseline included 83, 67, and 92 subjects in the guselkumab 100 mg q4w, guselkumab 100 mg q8w, and placebo groups, respectively.

Among these subjects, 34, 25, and 41 subjects in the guselkumab 100 mg q4w, guselkumab 100 mg q8w, and placebo groups, respectively also had pelvic x-ray confirmation at screening.

Change From Baseline in BASDAI Through Week 24

Among the 258 (34.9%) subjects with spondylitis and peripheral arthritis at baseline, a numerically greater reduction from baseline in BASDAI was observed in both guselkumab groups compared with the placebo group at each visit BASDAI was evaluated from Week 8 through Week 24.

At Week 24, a numerically greater reduction from baseline in BASDAI was observed in both the guselkumab 100 mg q4w group and the guselkumab 100 mg q8w group compared with the placebo group (both nominal $p<0.001$) based on the composite estimand.

Efficacy Data Through 1 Year from Studies CNTO1959PSA3001 and CNTO1959PSA3002

Efficacy and safety findings from studies PSA3001 and PSA3002 through 1 year of treatment became available during procedure and the MAH submitted new data with its D120 responses.

The Week 24 efficacy analyses across both Phase 3 PsA studies with guselkumab demonstrated that treatment with guselkumab 100 mg q8w and q4w led to clinically meaningful improvements across multiple PsA disease domains. Data through 1 year demonstrated maintenance of benefit across joint and skin responses, soft-tissue (ie, improvements in dactylitis and enthesitis), physical function (Disability Index of the Health Assessment Questionnaire [HAQ-DI] score) and health-related quality of life (eg, SF-36 Physical Component Summary [PCS], FACIT). In the majority of these clinical endpoints numerically greater clinical responses, which were generally comparable between the 2 dose groups, were observed at timepoints beyond Week 24 in those subjects who continued guselkumab q8w or q4w treatment through Week 52.

Table 12: Individual Study Efficacy Results at Week 52 for Studies CNTO1959PSA3001 and CNTO1959PSA3002

	CNTO1959PSA3001			CNTO1959PSA3002		
	Placebo→ guselkumab 100 mg q4w	Guselkumab 100 mg		Placebo→ guselkumab 100 mg q4w	Guselkumab 100 mg	
		q8w	q4w		q8w	q4w
Full Analysis Set 2	114	123	125	238	240	234
ACR Response at Week 52						
Subjects evaluable for ACR response at Week 52[a]	104	112	124	231	234	228
Subjects with an ACR 20 response at Week 52	71 (68.3%)	76 (67.9%)	94 (75.8%)	158 (68.7%)[b]	185 (79.1%)	173 (75.9%)
Subjects with an ACR 50 response at Week 52	38 (36.5%)	49 (43.4%)	69 (55.6%)	101 (43.7%)	120 (51.3%)	112 (49.1%)
Subjects with an ACR 70 response at Week 52	20 (19.2%)	33 (28.9%)	37 (29.8%)	44 (19.2%)[c]	69 (29.5%)	64 (28.1%)
Change from baseline in DAS28 (CRP) at Week 52						
Subjects with an observed change from baseline in DAS28 (CRP) at Week 52	103	112	123	228	234	227
Mean (SD) change from baseline in DAS28 (CRP) at Week 52	-1.84 (1.087)	-2.03 (1.250)	-1.99 (1.062)	-2.14 (1.142)	-2.08 (1.121)	-2.11 (1.128)
Minimal Disease Activity (MDA) Response at Week 52						
Subjects evaluable for MDA response at Week 52[d]	103	112	124	231	234	228
Subjects with an MDA response at Week 52	32 (31.1%)	38 (33.9%)	50 (40.3%)	73 (31.6%)	77 (32.9%)	84 (36.8%)
IGA Response at Week 52[e]						
Subjects evaluable for IGA response at Week 52[f]	65	75	88	172	170	173
Subjects with an IGA response at Week 52	53 (81.5%)	52 (69.3%)	73 (83.0%)	145 (84.3%)	131 (77.1%)	146 (84.4%)
PASI 90 Response at Week 52[e]						
Subjects evaluable for PASI 90 response at Week 52[g]	66	75	88	172	170	173
Subjects with a PASI 90 response at Week 52	48 (72.7%)	50 (66.7%)	67 (76.1%)	132 (76.7%)	131 (77.1%)	141 (81.5%)

[a] Subjects have an observed ACR response status.
[b] At Week 52, 230 subjects in the placebo guselkumab→100 mg q4w group evaluable for ACR 20 response at Week 52.
[c] At Week 52, 229 subjects in the placebo guselkumab→100 mg q4w group evaluable for ACR 70 response at Week 52.
[d] Subjects have an observed MDA response status.
[e] Among subjects who had ≥3% Body Surface Area (BSA) of Psoriatic Involvement and an IGA Score ≥2 (mild) at Baseline
[f] Subjects have an observed IGA response status. Note: IGA response is defined as IGA score of 0 or 1, and ≥2 grade reduction from baseline at the analysis visit.
[g] Subjects have an observed PASI response status.

Adapted from: [TEFACR01.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFACR01.SAS] 18DEC2019, 15:42; [TEFACR02.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFACR02.SAS] 18DEC2019, 15:42; [TEFACR03.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFACR03.SAS] 18DEC2019, 15:42; [TEFIGA01.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFIGA01.SAS] 18DEC2019, 15:45;[TEFPASI05.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFPASI05.SAS] 18DEC2019, 15:45; [TEFDAS01.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFDAS01.SAS] 18DEC2019, 15:43; [TEFMDA01.RTF] [CNTO1959\PSA3001\DBR_WEEK_60\RE_WEEK_60\PROD\TEFMDA01.SAS] 18DEC2019, 23:00; TEFACR01.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFACR01.SAS] 10OCT2019, 16:31; [TEFACR02.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFACR02.SAS] 10OCT2019, 16:31; [TEFACR03.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFACR03.SAS] 10OCT2019, 16:31; [TEFDAS01.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFDAS01.SAS] 10OCT2019, 16:34; [TEFMDA01.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFMDA01.SAS] 10OCT2019, 16:42; [TEFPASI05.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFPASI05.SAS] 10OCT2019, 16:43; [TEFIGA01.RTF] [CNTO1959\PSA3002\DBR_WEEK_52\RE_WEEK_52\PROD\TEFIGA01.SAS] 10OCT2019, 16:38

Summary of the Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) by Visit Through Week 24, Based on the Composite Estimand Using an MMRM Model; Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis at Baseline (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis at Baseline	99	73	86
Subjects with a baseline BASDAI = 0[a,b]	0	0	0
Subjects with a baseline BASDAI > 0[a,b]	92	67	83
Week 8			
Subjects evaluable[b]			
N	92	66	82
Mean (SD)	-0.790 (1.8049)	-1.602 (2.2637)	-1.582 (1.7255)
Median	-0.765	-1.120	-1.370
Range	(-6.67; 3.24)	(-8.46; 4.54)	(-6.42; 1.56)
IQ range	(-1.900; 0.510)	(-2.550; 0.040)	(-2.510; -0.130)
Model Based Estimates of the Mean Change[a,c]			
LSMean (95% CI)[d]	-0.645 (-1.039, -0.251)	-1.429 (-1.914, -0.944)	-1.523 (-1.937, -1.109)
LSMean difference (95% CI)		-0.784 (-1.347, -0.220)	-0.878 (-1.404, -0.352)
p-value[d]		0.007	0.001
Week 16			
Subjects evaluable[b]			
N	92	66	81
Mean (SD)	-1.168 (2.1668)	-2.312 (2.5152)	-2.265 (1.9895)
Median	-0.810	-2.105	-2.060
Range	(-7.93; 2.91)	(-7.07; 2.65)	(-7.62; 2.50)
IQ range	(-2.610; 0.270)	(-4.240; -0.440)	(-3.510; -0.950)
Model Based Estimates of the Mean Change[a,c]			
LSMean (95% CI)[d]	-1.023 (-1.466, -0.580)	-2.139 (-2.680, -1.597)	-2.207 (-2.675, -1.740)
LSMean difference (95% CI)		-1.115 (-1.761, -0.470)	-1.184 (-1.789, -0.579)
p-value[d]		< 0.001	< 0.001
Week 24			
Subjects evaluable[b]			
N	92	65	82
Mean (SD)	-1.369 (2.3488)	-2.589 (2.4080)	-2.560 (2.0137)
Median	-0.770	-2.180	-2.535
Range	(-9.12; 3.19)	(-8.19; 1.07)	(-7.30; 1.09)
IQ range	(-2.885; 0.020)	(-4.150; -0.610)	(-4.190; -1.060)
Model Based Estimates of the Mean Change[a,c]			
LSMean (95% CI)[d]	-1.224 (-1.681, -0.767)	-2.431 (-2.989, -1.873)	-2.500 (-2.981, -2.019)
LSMean difference (95% CI)		-1.207 (-1.877, -0.538)	-1.276 (-1.902, -0.651)
p-value[d]		< 0.001	< 0.001

TEFBASDAI09: Number of Subjects Who Achieved ≥ 50% Improvement from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) by Visit Through Week 24, Based on the Composite Estimand; Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis and BASDAI Score >0 at Baseline (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis and BASDAI Score >0 at Baseline	92	67	83

Week 24			
Subjects evaluable for achieving 50% improvement from baseline in BASDAI[a]	92	65	82
Subjects who achieved 50% improvement from baseline in BASDAI[b,h]	20 (21.7%)	26 (40.0%)	31 (37.8%)
All subjects (including those with imputed data)	92	67	83
Subjects who achieved 50% improvement from baseline in BASDAI[b,c,h]	20 (21.7%)	26 (38.8%)	31 (37.3%)
% Difference (95% CI)[d]		15.0 (0.4, 29.6)	15.6 (2.4, 28.8)
p-value[e]		0.048	0.024

Regarding the clinically meaningful improvement of change in BASDAI score ≥2,it is the Applicant's understanding that this references a decrease of ≥2 points at the individual subject level (20 mm on a 100 mm visual analogue scale), and not a difference of ≥2 points between the mean changes of groups of subjects. New analyses were performed to identify the number and percent of subjects with an improvement in BASDAI of ≥2 points from baseline.

The results from each study and from the pooled studies are shown in Table 24 below. In both the individual and pooled studies, greater proportions of subjects in the guselkumab groups achieved the clinically meaningful improvement in BASDAI of ≥2 points from baseline compared with the placebo group. Although there was a difference in the placebo response rates between the 2 studies, no apparent differences were observed in the response rates between the guselkumab q8w and q4w dose groups or across the 2 studies.

Table 24: Number of Subjects Who Achieved ≥2 Point Improvement from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24, Based on the Composite Estimand; Full Analysis Set 1, Among the Subjects With Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	CNTO1959PSA3001			CNTO1959PSA3002			2-Study Combined		
		Guselkumab			Guselkumab			Guselkumab	
	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1 Among the Subjects with Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline	22	24	18	92	65	82	114	89	100
Subjects evaluable for achieving ≥2 Point Improvement in BASDAI at Week 24[a]	22	24	18	92	65	82	114	89	100
Subjects who achieved ≥2 Point Improvement in BASDAI	4 (18.2%)	14 (58.3%)	10 (55.6%)	29 (31.5%)	35 (53.8%)	49 (59.8%)	33 (28.9%)	49 (55.1%)	59 (59.0%)
95% CI of response rate[b]	(0.0%, 36.6%)	(36.5%, 80.1%)	(29.8%, 81.3%)	(21.5%, 41.6%)	(41.0%, 66.7%)	(48.5%, 71.0%)	(20.2%, 37.7%)	(44.2%, 66.0%)	(48.9%, 69.1%)
Difference (95% CI) in response rates[b]		37.7 (10.9, 64.5)	35.5 (6.2, 64.8)		18.6 (3.1, 34.1)	28.0 (14.1, 41.9)		22.8 (9.4, 36.3)	29.5 (16.7, 42.3)
p-value[c]		0.015	0.035		0.023	< 0.001		0.002	< 0.001

Table 24: Number of Subjects Who Achieved ≥2 Point Improvement from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24, Based on the Composite Estimand; Full Analysis Set 1, Among the Subjects With Spondylitis and Peripheral Arthritis and BASDAI Score ≥2 at Baseline (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	CNTO1959PSA3001			CNTO1959PSA3002			2-Study Combined		
		Guselkumab			Guselkumab			Guselkumab	
	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w	Placebo	100 mg q8w	100 mg q4w
Difference (95% CI) in response rates[d]			-2.8			7.7			4.9
			(-33.0, 27.5)			(-8.3, 23.6)			(-9.2, 19.0)
p-value[e]			0.948			0.359			0.438

[a] The estimand is defined as responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed. Subjects with data missing were considered non-responders.
[b] The confidence intervals (CIs) for response rates and for difference in response rates between guselkumab group vs the placebo group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
[c] The p-value comparing the guselkumab group vs the placebo group was based on the CMH test if the Mantel Fleiss criterion was satisfied. Otherwise, the Fisher's exact test was used. The symbol "†" was attached as a superscript to those p-values that were based on the Fisher's exact test.
[d] The confidence intervals (CIs) for difference in response rates between guselkumab 100 mg q4w group vs 100 mg at Weeks 0, 4, and then q8w group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
[e] The p-values comparing between guselkumab 100 mg q4w group vs 100 mg at Weeks 0, 4, and then q8w group were based on the CMH test if the Mantel Fleiss criterion was satisfied. Otherwise, the Fisher's exact test was used. The symbol "†" was attached as a superscript to those p-values that were based on the Fisher's exact test.
The BASDAI is based on 6 questions relating to 5 major symptoms of ankylosing spondylitis through a patient's self assessment. A higher score indicates greater disease severity.

[EMA_TEFBAS05S12.RTF] [CNTO1959\Z_ADHOC_REQ\DBR_PSA_SBLA\RE_EMA_20191223\PROD\EMA_TEFBAS05S12.SAS] 18FEB2020, 13:14

Subpopulation Analyses for the Pooled Phase 3 Studies

With a few exceptions, subpopulation (subgroup) analyses generally showed similar ACR responses between various subgroups. Therefore, only the subgroups with ACR response deviations are presented below.

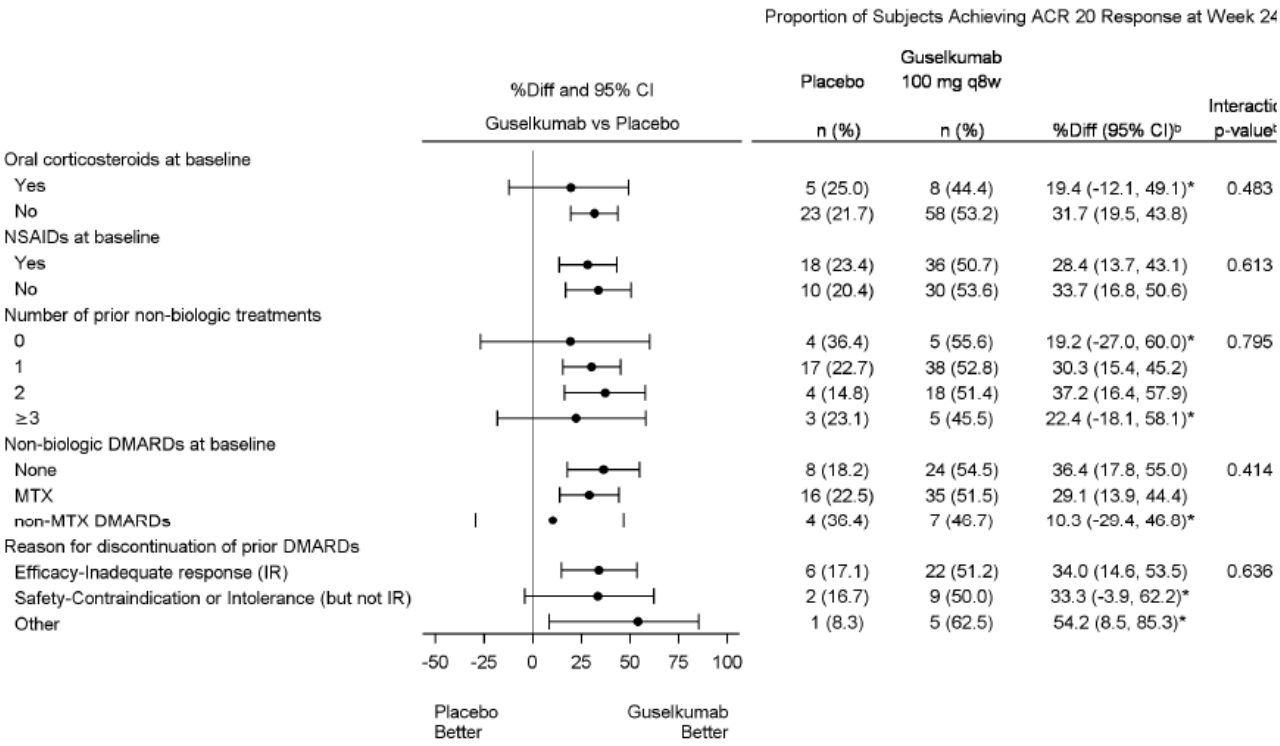
For diabetes status, consistently higher ACR 20, ACR 50, and ACR 70 responses were observed over time in the guselkumab groups compared with the placebo group, regardless of diabetes status. For ACR 20 and 50, response rates trended higher in subjects with diabetes compared with those without diabetes, while results were generally comparable for ACR 70. Results were generally comparable for the guselkumab 100 mg q8w and q4w groups across ACR responses within each subgroup.

For BMI categories, there were no different response on ACR20 endpoint by BMI categories in the Phase-3 PSA studies.

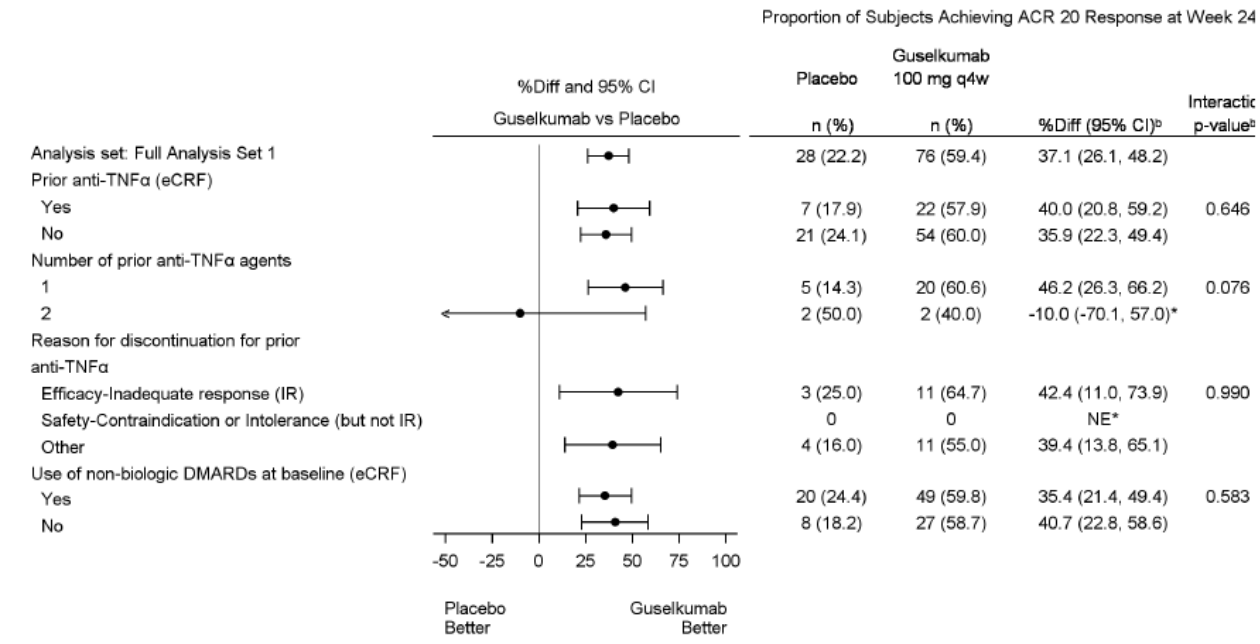
For baseline DMARD and MTX use, subgroup of subjects achieving an ACR 20 response in both guselkumab groups group were comparable with results on subjects not receiving DMARDs at BL.

For *baseline DMARD use*, subgroup of subjects achieving an ACR 50 response in the q8w group who were receiving a DMARD at baseline was somewhat smaller (28.5%) compared with subjects not receiving DMARDs at BL (36.1%).

For *baseline MTX use*, subgroup of subjects achieving an ACR 50 response in the q8w group who were receiving MTX at baseline was somewhat smaller (26.8%) compared with subjects not receiving MTX at BL (36.1%).



According to the pooled subgroup analysis, prior TNF alfa i use seemed to have no effect on ACR response rates. (In this analysis, TNF-alfa i naive patients from PSA3001 and patients from PSA3002 were pooled.)



Clinical studies in special populations

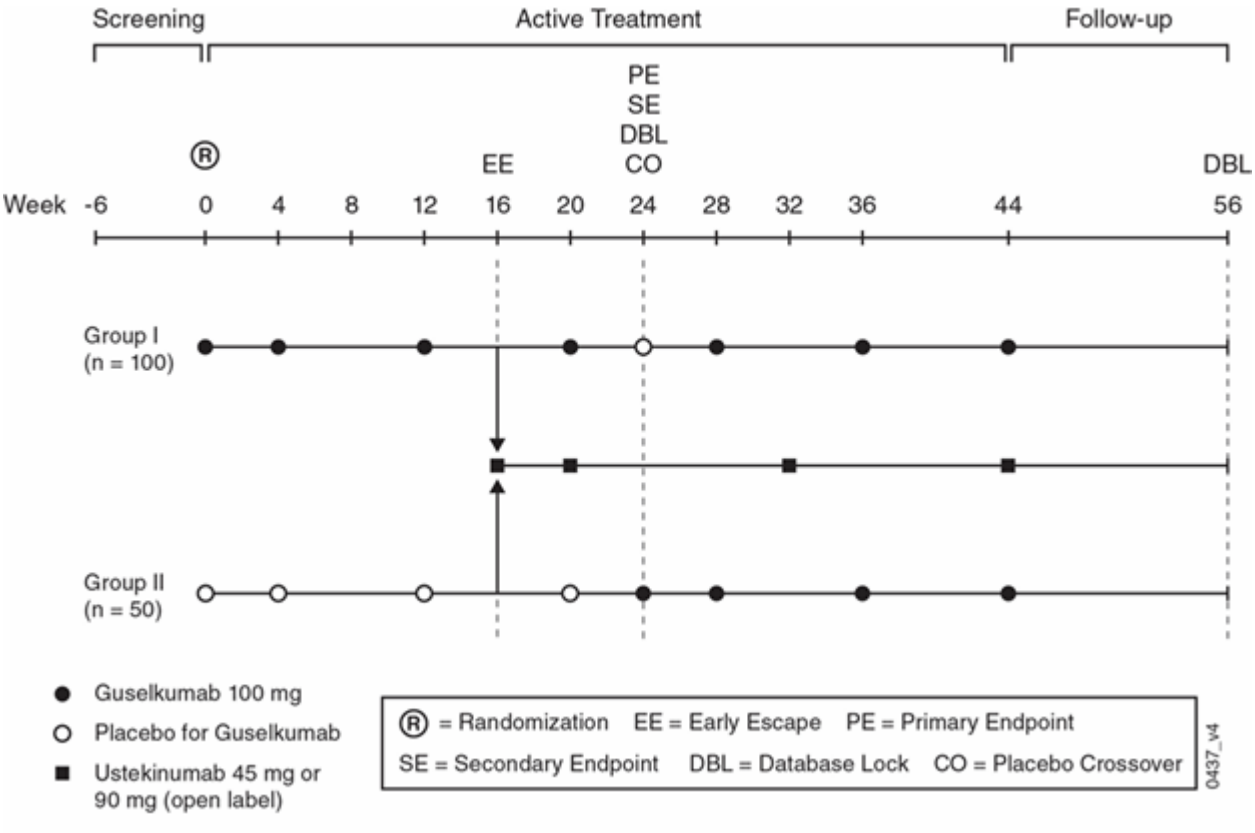
No clinical studies in special populations were submitted this was considered acceptable by the CHMP.

Supportive study(ies)

Phase 2 Psoriatic Arthritis Study CNTO1959PSA2001

A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab in the Treatment of Subjects With Active Psoriatic Arthritis

Figure 5.4.2.11 Study Schema for the Phase 2 PsA Study CNTO1959PSA2001



Methods

Study participants

Subjects eligible for the study were adult men or women at least 18 years of age with active PsA for at least 6 months prior to the first administration of study drug who meet ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria at screening. They had an inadequate response to current or prior standard therapies (eg, MTX, corticosteroids). Subjects must have symptoms of active PsA at screening and baseline and have a C-reactive protein (CRP) level of ≥0.3 mg/dL at screening. Subjects must not have been treated with guselkumab or ustekinumab in the past. Subjects must have had plaque psoriasis in at least 3% of BSA Subjects with prior biologic treatments (other than 1 anti-TNFα agent) or JAK-inhibitors for PsA or psoriasis were excluded, including but not limited to guselkumab, ustekinumab, or any other therapeutic agent targeted at IL-12, IL-17, or IL-23. Up to 20% of subjects with prior exposure to 1 anti-TNFα agent were permitted. Anti-TNFα agents received prior to the study entry must have been washed out within 8 weeks (adalimumab, golimumab SC, certolizumab pegol or etanercept or biosimilars to these

agents) or 12 weeks (infliximab [or its biosimilars] or golimumab IV) before the first study agent administration.

Approximately 150 subjects who satisfied all inclusion and exclusion criteria were to be randomized using permuted block randomization stratified by prior anti-TNF use in a 2:1 ratio to receive either guselkumab 100 mg or placebo SC at Weeks 0, 4, 12, and 20. Subjects with prior exposure to 1 anti-TNFα agent were permitted but limited to 20% of the study population. A stable dose of MTX, oral corticosteroids, or NSAIDs/analgesics was permitted but not required during the study. At Week 24, subjects randomized to placebo crossed over to guselkumab and receive guselkumab 100 mg at Weeks 24, 28, 36 and 44. Subjects randomized to guselkumab received a placebo injection at Week 24, then continued to receive guselkumab at Weeks 28, 36 and 44. Subjects in both treatment groups who had <5% improvement from baseline in both tender and swollen joint counts at Week 16 qualified for early escape (EE) and received open-label ustekinumab (STELARA®) 45 mg or 90 mg at Weeks 16, 20, 32, and 44 based on the approved dosage for the PsA indication in the particular country of study. There was a post treatment follow-up period from Week 44 to Week 56. Database locks were at Weeks 24 and 56.

Results

Participant flow

Table 5.4.2.30 Number of Subjects by Study Treatment Assigned vs Study Treatment Received through Week 44; Full Analysis Set (Study CNTO1959PSA2001)

	Placebo	Guselkumab
Analysis set: Full Analysis Set	49	100
Subjects treated	49	100
Treatment received		
Placebo[a]	3 (6.1%)	0
Placebo → Ustekinumab at Week 16[b]	17 (34.7%)	0
Placebo → Guselkumab at Week 24[c]	29 (59.2%)	0
Guselkumab[d]	0	90 (90.0%)
Guselkumab → Ustekinumab at Week 16[b]	0	10 (10.0%)

[a] Subjects who received placebo only.
[b] Subjects who early escaped at Week 16.
[c] Subjects who crossed over to guselkumab at Week 24.
[d] Subjects who received Guselkumab only.

Table 5.4.2.31 Number of Subjects Who Discontinued Study Agent through Week 44; Full Analysis Set (Study CNTO1959PSA2001)

	Placebo[a]	Crossover (Placebo → Guselkumab)[b]	Guselkumab[a]	Early Escape (Placebo → Ustekinumab)[c]	Early Escape (Guselkumab → Ustekinumab)[c]	Total
Analysis set: Full Analysis Set	49	29	100	17	10	149
Subjects who discontinued study agent	3 (6.1%)	1 (3.4%)	6 (6.0%)	2 (11.8%)	1 (10.0%)	13 (8.7%)
Reason for discontinuation	0	0	0	0	0	0
Adverse event	0	0	2 (2.0%)	0	0	2 (1.3%)
Worsening of psoriasis	0	0	0	0	0	0
Worsening of psoriatic arthritis	0	0	0	0	0	0
Worsening of psoriasis and psoriatic arthritis	0	0	0	0	0	0
Other Adverse Event	0	0	2 (2.0%)	0	0	2 (1.3%)
Initiated prohibited medication	0	0	0	0	0	0
Death	0	0	0	0	0	0
Lack of Efficacy	2 (4.1%)	0	1 (1.0%)	2 (11.8%)	1 (10.0%)	6 (4.0%)
Lost to follow-up	1 (2.0%)	0	0	0	0	1 (0.7%)
Non-compliance with study drug	0	0	0	0	0	0
Product quality compliant	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Trial site terminated by sponsor	0	0	0	0	0	0
Withdrawal by subject	0	1 (3.4%)	2 (2.0%)	0	0	3 (2.0%)
Pregnancy	0	0	0	0	0	0
Other	0	0	1 (1.0%)	0	0	1 (0.7%)

Recruitment

A total of 149 subjects were enrolled at 34 sites in 7 countries: Canada (n=6), Germany (n=4), Poland (n=25), Romania (n=5), Russia (n=89), Spain (n=9), and the US (n=11).

The study was initiated on 27 March 2015 when the first subject consented to participate in the study. The last study-related procedure was performed on 17 January 2017.

Baseline data

Study PSA2001 randomly assigned a total of 149 subjects across 2 treatment groups with 100 subjects in the guselkumab 100 mg group and 49 subjects in the placebo group. The demographic characteristics of the enrolled population were generally well balanced between randomized groups . All subjects were white and 51.0% of the subjects were male. The median age was 47.0 years and the median weight was 82.0 kg.

Baseline disease characteristics were similar across treatment groups and indicative of a study population with active PsA. The most prevalent PsA subtypes were polyarticular arthritis with no rheumatoid nodules (39.6%) and asymmetric peripheral arthritis (26.8%). Similar to other PsA populations, the median duration of psoriasis (12.8 years) was substantially greater than the median duration of PsA (4.0 years). The ACR core set of outcome measurements were indicative of subjects with active PsA and were generally comparable across the treatment groups. Subjects had median numbers of swollen and tender joints of 9.0 and 17.0, respectively, a median HAQ-DI score of 1.5, and a median CRP of 0.91 mg/dL. At baseline, 54.4% of subjects had dactylitis with a mean score (1-60) of 5.7 and 71.8% of subjects had enthesitis at baseline, with a mean enthesitis score (1-6) of 2.7. Subjects had a median percent of BSA skin involvement of 10.0% and the median PASI score was 7.85. Mean BSA and PASI were higher in the guselkumab group (17.2 and 12.03, respectively) compared to the placebo group (13.6 and 9.88, respectively). a higher proportion in the guselkumab group had hand/foot psoriasis (45.0% vs 34.7% in the placebo group).A higher proportion of subjects in the guselkumab group reported DIP joint arthritis (63.0% vs 44.9% in the placebo group) and asymmetric peripheral arthritis (61.0% vs 46.9% in the

placebo group). More subjects in the guselkumab group (6 [6.0%]) than in the placebo group (1 [2.0%]) reported prior joint procedures,

At baseline, 44.3% of subjects were taking MTX at a median dose of 15.0 mg/week and 13.4% of subjects were taking oral corticosteroids at a median dose of 6.25 mg/day. A majority of subjects (71.1%) were taking NSAIDs at baseline and 87.9% of subjects had prior DMARD experience. A total of 13 subjects (8.7%) had prior exposure to anti-TNFα therapies

Numbers analysed

Through Week 24, the efficacy analysis data set (Full Analysis Set) included all subjects who were randomized into the study and received at least 1 administration of study treatment (guselkumab or placebo), ie, modified Intent-to-Treat population.

Table5.4.2.32 Summary of Subjects per Analysis Set; All subjects (Study CNTO1959PSA2001)

	Placebo	Guselkumab	Total
Status			
Screened	NA	NA	251
Not Randomized	NA	NA	102
Randomized	49	100	149
Treated (Safety Analysis Set)	49	100	149
Randomized and treated (Full Analysis Set)	49	100	149
Qualified for Early Escape	17	10	27

Table5.4.2.33 Number of Subjects by Study Treatment Assigned vs Study Treatment Received Prior to Week 24 Study Agent Administration; Full Analysis Set (Study CNTO1959PSA2001)

	Placebo	Guselkumab
Analysis set: Full Analysis Set	49	100
Subjects treated	49	100
Treatment received		
Placebo[a]	3 (6.1%)	0
Placebo → Ustekinumab at Week 16[b]	17 (34.7%)	0
Placebo → Guselkumab at Week 24[c]	29 (59.2%)	0
Guselkumab[d]	0	90 (90.0%)
Guselkumab → Ustekinumab at Week 16[b]	0	10 (10.0%)

[a] Subjects who received placebo only.
[b] Subjects who early escaped at Week 16.
[c] Subjects who crossed over to guselkumab at Week 24.
[d] Subjects who received Guselkumab only.

After Week 24 through Week 56, the efficacy analysis set included all randomized subjects who did not EE to ustekinumab at Week 16 and who did not discontinue study treatment prior to or at Week 24, which is referred to as Post Week 24 Efficacy Analysis Set:

- *Crossover (Placebo → Guselkumab) (n=29)*: All subjects who were randomized to placebo and crossed over to receive guselkumab at Week 24.
- *Guselkumab (n=86)*: All subjects who were randomized to guselkumab and did not EE at Week 16 or discontinue study treatment prior to or at Week 24.

Outcomes and estimation

Improvement in Signs and Symptoms of Psoriatic Arthritis

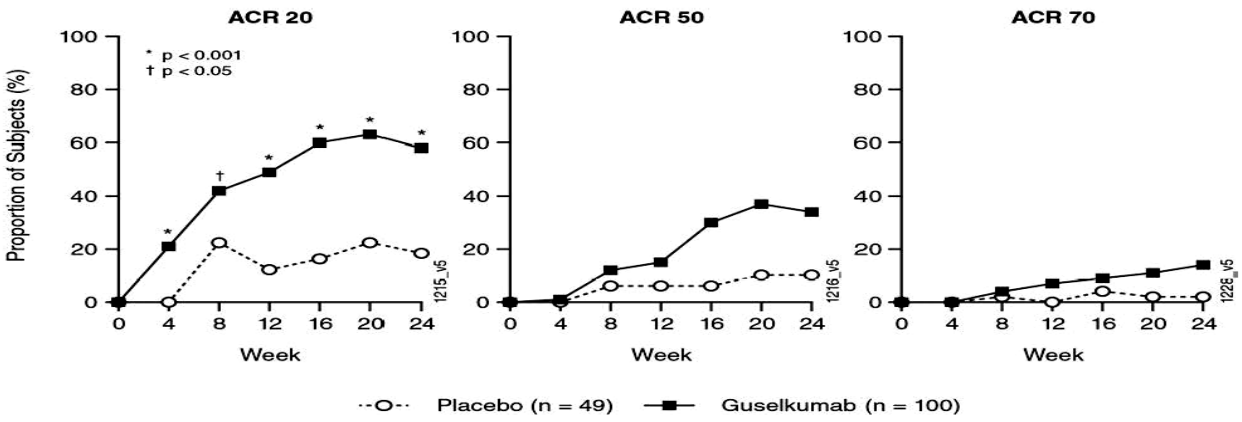
Table 5.4.2.34: Summary of Efficacy Results for Endpoints Related to Signs and Symptoms of PsA and Skin Disease at Week 24 (CNTO1959PSA2001)

Efficacy Endpoints	Placebo	Guselkumab	p-value[c]
Proportion of subjects with an:			
ACR 20	18.4%	58.0%	p<0.001[d]
ACR 50	10.2%	34.0%	p=0.002
ACR 70	2.0%	14.0%	p=0.023 (post-hoc)
PASI 75	12.5%	78.6%	p<0.001[d]
PASI 90	6.3%	66.3%	p<0.001
PASI 100	6.3%	39.8%	p<0.001
Median percent change from baseline in Leeds Enthesitis Index (LEI)[a]	-33.33%	-100.00%	p=0.009
Proportion of subjects with resolution of enthesitis[a]	29.0%	56.6%	p=0.012
Median percent change from baseline in dactylitis[b]	-33.33%	-100.00%	p<0.001
Proportion of subjects with resolution of dactylitisi[b]	17.4%	55.2%	p=0.001
Proportion of subjects achieving Minimal Disease Activity (MDA)	2.0%	23.0%	p=0.001

[a]Among the subjects with enthesitis at baseline (Placebo: N=31; Guselkumab: N=76)
[b]Among the subjects with dactylitis at baseline (Placebo: N=23; Guselkumab: N=58)
[c] all p-values are nominal.
[d] Multiplicity-controlled p-value.
Key: ACR = American College of Rheumatology; PASI = psoriasis area and severity index; PCS = physical component summary; SD = standard deviation;

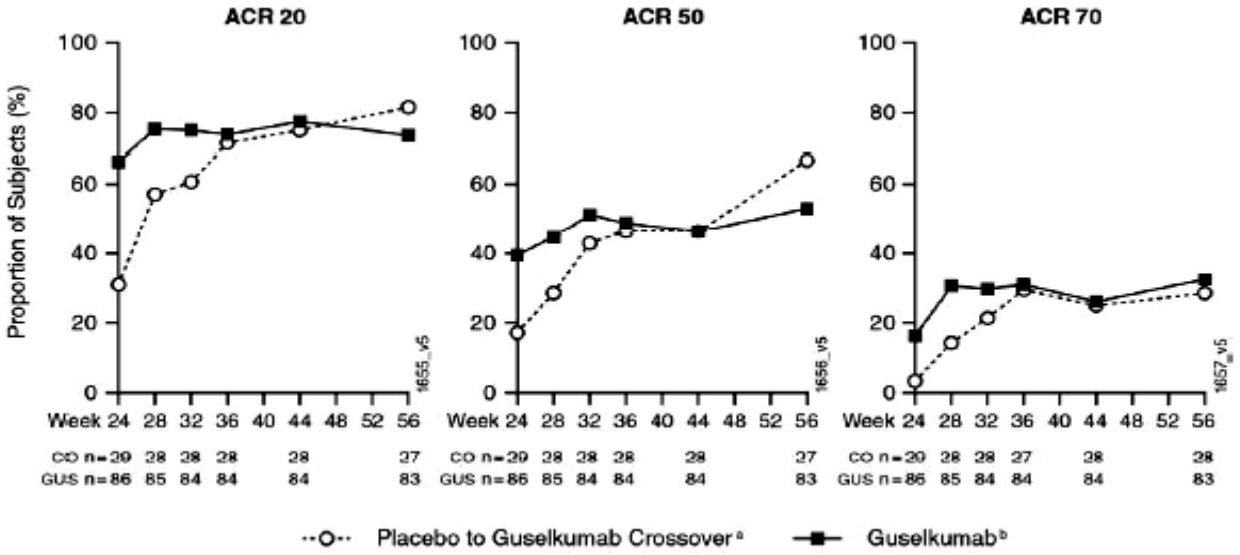
Greater proportions of subjects with an ACR 20 response were observed in the guselkumab group as early as Week 4 (21% versus 0 in the placebo group, nominal p<0.001).

Figure 5.4.2.12 Proportion of Subjects Who Achieved an ACR 20, ACR 50 and ACR 70 Response through Week 24; Full Analysis Set (Study CNTO1959PSA2001)



Therapeutic responses from Week 24 through Week 56, Guselkumab, and Crossover (switched from Placebo to Guselkumab at Week24) treatment groups

Figure 5.4.2.13 Proportion of Subjects Who Achieved an ACR 20, ACR 50 and ACR 70 Response from Week 24 through Week 56; Post Week 24 Efficacy Analysis Set (Study CNTO1959PSA2001)



In guselkumab patients, further improvement on ACR 20, ACR 50, and ACR 70 response rates from Week 24 was observed, and the improvement was maintained through Week 44 (77.4%, 46.4%, and 26.2%, respectively).

For placebo → guselkumab crossover group patients, rapid improvement on ACR 20, ACR 50, and ACR 70 response rates was observed at Week 28 compared to Week 24, 4 weeks after receiving the first injection of guselkumab. Improvement continued over time and by Week 44, the ACR 20, ACR 50, and ACR 70 response rates (75.0%, 46.4%, and 25.0%, respectively) were numerically comparable to those in the guselkumab group (Figure 5.4.2.13.).

For subjects in the *guselkumab group*, the proportion of subjects with unresolved enthesitis was 38.8% at Week 24 and it was maintained through Week 44 (37.9%) and through Week 56.

For subjects in the *placebo → guselkumab crossover group*, the proportion of subjects with unresolved enthesitis was 66.7% at Week 24, 35.3% at Week 32. After some increase through Week 44 (47.1%) it decreased again through Week 56 (37.5%).

For subjects in the *guselkumab group*, the proportion of subjects with unresolved dactylitis was 40.0% at Week 24 and 20.4% at Week 44, maintained through Week 56.

For subjects in the *placebo → guselkumab crossover group*, the proportion of subjects with unresolved dactylitis was 81.3% at Week 24, 62.5% at Week 28, and 6.3% at Week 56.

For subjects in the *guselkumab group*, PASI 50, PASI 75, PASI 90, and PASI 100 responses at Week 44 were 94.0%, 90.4%, 81.9%, and 63.9%, respectively at Week 44. The skin response was maintained through Week 56.

For subjects in the *placebo → guselkumab crossover group*, PASI 50, PASI 75, PASI 90, and PASI 100 response rates were 37.9%, 20.7%, 10.3%, and 10.3%, respectively at Week 24, 60.7%, 35.7%, 25.0%, and 17.9%, respectively at Week 28, 4 weeks after the first injection of guselkumab. At Week 44,

the PASI 50, PASI 75, PASI 90, and PASI 100 response rates were 89.3%, 82.1%, 75.0%, and 67.9%, respectively. The improvement was maintained through Week 56.

For subjects in the *guselkumab group*, the proportion of subjects achieving MDA was 24.4% at Week 24, reached the maximum at Week 32 (35.7%) and was well maintained through Week 44 (33.3%) and Week 56.

For subjects in the *placebo → guselkumab crossover group*, only one subject (3.4%) achieved MDA at Week 24 prior to receiving guselkumab. After the switch, 14.3% and 28.6% of these patients achieved MDA at Week 28 and Week 44, respectively. Further remarkable improvement could be observed through Week 56 with 44.4% of the crossover subjects achieving MDA.

Improvement in Physical Function

At baseline, both the placebo and the guselkumab groups had a similar HAQ-DI. The change from baseline in HAQ-DI at Week 24 was significantly greater in the guselkumab group compared with the placebo group (mean: -0.42 and -0.06, respectively; adjusted $p<0.001$.

Improvement in Health-related Quality of Life

At Week 24, the change from baseline in SF-36 PCS was greater in the guselkumab group (mean: 6.59) compared with the placebo group (mean: 0.46, nominal $p<0.001$); the mean change from baseline in SF-36 MCS was 4.95 in the guselkumab group compared with 0.42 in the placebo group (nominal $p=0.002$). The improvements were well maintained through Week 44 and Week 56.

Subgroup Analyses

Consistency of treatment effect for the primary endpoint of ACR 20 at Week 24 was examined across:

- Baseline demographic and geographic subgroups ,
- Baseline disease characteristics subgroups,
- Prior or concomitant medication use subgroups

In subgroup analyses, significantly or numerically higher treatment effect was observed in the guselkumab group on the primary endpoint ACR20 for almost subgroups. The exceptions were few subgroups in which a small sample size limited the interpretation. According to the Applicant's explanation, these effects had similar route cause: namely, the low patient number coupled with a higher placebo effect in some of the concerned subgroups.

Efficacy and Immunogenicity

To evaluate the impact of antibodies to guselkumab on clinical efficacy in study PSA2001, ACR responses and PASI responses were evaluated according to antibody status for all subjects with appropriate samples. The incidence of antibodies to guselkumab was 4.7% (6/128) through Week 44 and Week 56.

For subjects who were positive for antibodies to guselkumab through Week 44, the presence of antibodies to guselkumab had no apparent impact on ACR 20 or ACR 50 responses or PASI 75 response. However, it should be noted that the number of subjects who were positive for antibodies to guselkumab was too small (n=6) to draw any conclusion on the effect of antibody development on clinical efficacy.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Tremfya (guselkumab) is already approved for the treatment of plaque psoriasis. Now, the MAH seeks for an approval of an extended indication for guselkumab alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

Recommendations of the EMA guideline (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriatic arthritis, CHMP/EWP/438/04) have mostly been taken into account. The MAH did not seek Scientific Advice from either EMA or NCAs. The clinical development program includes one completed Phase 2 study (PSA2001), and two global Phase 3 studies (PSA3001 and PSA3002 (ongoing)) in subjects with active PsA. This submission contains efficacy and safety data through Week 56 of guselkumab treatment from the Phase 2 trial and mainly 24 week-data from the two Phase 3 trials. With the responses to the first RSI, the MAH provided preliminary efficacy and safety data from phase 3 studies through week 52.

The three PsA studies included a target population of adult subjects diagnosed with active PsA for at least 6 months prior to the first administration of study agent and who met ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening. Active PsA was defined in studies PSA2001 and PSA3001: ≥3 swollen joints, ≥3 tender joints, and a C-reactive protein (CRP) level of ≥0.3 mg/dL; in study PSA3002: ≥5 swollen joints, ≥5 tender joints, and a C-reactive protein (CRP) level of ≥0.6 mg/dL. Subjects must have had inadequate response or evidence of intolerance to current or previous PsA treatments including non-biologic disease-modifying antirheumatic drugs (DMARD) treatment (≥3 months), apremilast (≥4 months), and/or nonsteroidal anti-inflammatory drug (NSAID) therapy (≥4 weeks) prior to the first administration of study agent.

Subjects with prior exposure to anti-tumour necrosis factor alpha (TNFα) agents were allowed in studies PSA2001 (1 anti-TNFα agent limited to 20% of the study population) and PSA3001 (up to 2 anti-TNFα agents and limited to approximately 30% of the study population). Subjects in study PSA3002 were required to be biologic-naïve and with higher PsA activity. The requirements for a fully biologic naïve population in this study, along with higher CRP levels and higher joint counts compared with other studies (PsA2001 and PsA3001), were selected in order to enrol a population appropriate for assessment of radiographic progression and to increase the power for detection of a treatment effect for guselkumab on the radiographic endpoints.

Based upon the clinical efficacy, safety, pharmacokinetic (PK) data, and exposure-response modeling analysis using data from the Phase 2 study of guselkumab in subjects with PsA, 2 guselkumab s.c. dose regimens were chosen for evaluation in the guselkumab Phase 3 PsA program: 100 mg s.c. at Weeks 0 and 4, then q8w thereafter (q8w), i.e. the same as for approved for plaque psoriasis OR 100 mg s.c. q4w.

In the Phase 2 study subjects were randomised in 1:2 ratio to placebo or to guselkumab q8w, through Week 44. At Week 24, subjects on placebo were crossed over to double blind guselkumab through week 52.

In the Phase 3 studies, patients were randomised in 1:1:1 ratio to placebo or to one of the guselkumab treatment groups q8w or q4w. Randomization was stratified by baseline non-biologic DMARD use in both Phase 3 studies. In addition, randomization was also stratified by prior exposure to anti-TNFα agents in study PSA3001 and in addition by CRP (<2.0 mg/dL or ≥2.0mg/dL) in study PSO3002.

At Week 16, all subjects with <5% improvement from baseline in both tender and swollen joint counts were considered as meeting EE criteria and received open-label ustekinumab in Study PsA2001 or

remained on the dosing regimen they were randomized to at Week 0 and allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum allowed dose specified in the protocol in studies PsA3301 and PsA3002.

At Week 24, subjects on placebo were crossed over to double blind guselkumab q4w. This study design hampers robust assessment of efficacy and safety, as it allows evaluation effects to placebo only short-term (week 24) and not until one year. However, the CHMP understand the rationale of this design from an ethical perspective.

For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

The full length of the treatment period of the Phase-3 studies will be 48 weeks with a final efficacy visit at Week 52 and an 8-week follow-up through Week 60.

Key secondary endpoints included IGA, DAS 28 (CRP), HAQDI as well as higher ACR responses 50, 70, effects on BASDAI, dactylitis, enthesitis and QoL. In study 3002 an additional key secondary endpoint was the change from baseline in modified vdH-S score at Week 24.

Neither pivotal studies in PsA had an active control arm but placebo control is acceptable to the CHMP. At the CHMP's request, the Applicant provided skin psoriasis-related efficacy data from guselkumab PSO studies PSO3001, 3002, 3003 and 3009 for PSO patients with history of PsA. In these Phase-3 PSO studies patients reported about their PsA diagnosis at the screening. There was no information provided in the CSRs of Phase 3 PSO studies whether or not patients with PsA diagnosis met the CASPAR criteria of active PsA at the screening/BL.

The efficacy assessments included standard and approved measures of the signs and symptoms of PsA, including assessment of effect in soft tissue involvements (enthesitis and dactylitis) and axial manifestations. Inhibition of structural damage by using usual radiographic endpoints was also assessed, together with physical function, psoriatic skin, nail and scalp manifestations, health-related quality of life and health economics assessments.

Subgroup analyses were performed for the primary endpoint of the proportion of subjects who achieved an ACR 20 response at Week 24 over baseline demographics, baseline disease characteristics, and prior and baseline medication use.

Design and conduct of clinical studies were overall considered acceptable to the CHMP.

Efficacy data and additional analyses

Phase 2 study included 149 patients while Phase 3 studies 360 and 684 patients, into studies PSA3001 and PSA3002, respectively.

Overall completion rates were high in phase 3 studies: more than 97% of guselkumab-patients completed studies, among patients with placebo the discontinuation rates were 7 and 0.8% in PSO3001 and 3002 studies, respectively. More subject with placebo-treatment had an early escape: around 3% and 5% in guselkumab-arms, 15 % and 19% in placebo-arms in PSO3001 and 3002, respectively. Completion of Phase 2 trial was similarly high but considerably more subjects had early escape at week 16: 35% and 10% for placebo and guselkumab, respectively. Negligible proportion of subjects dropped out due to lack of efficacy and proportion of early escape -patients were generally low with the active treatment. Proportion of patients with treatment failure with guselkumab in the phase 3 studies were low (cca 2-5% in guselkumab-arms), however, treatment failure rates differed considerably across studies for placebo-patients: 16.7% vs. 6.9% in studies PSA3001 and 3002, respectively. The MAH explained it with differences in treatment duration, differences in number of subjects with prior bDMARD and TNF-alfa

inhibitor experiences (prior bDMARD medication incl. TNF-alfa I agents was allowed in Study PSA3001 only) and differences in ACR 20 response rate in the placebo groups of studies PSA3001 and 3002. This was considered acceptable to the CHMP.

In PSA3001, Baseline BSA and PASI measurements suggested the guselkumab 100 mg q4w group had more severe psoriasis compared to the guselkumab 100 mg q8w group and the placebo group. In addition, the proportion of subjects with IGA ≥2 (mild to severe) was higher in the guselkumab 100 mg q4w group (85.9%) compared to the guselkumab 100 mg q8w group (78.7%) and placebo (73.0%).

In the Phase 3 studies, a significantly greater proportion of subjects met the criteria for ACR 20 response at week 24 in the guselkumab groups, compared to the placebo group. The ACR20 responder rates were clinically relevant: cca. 29% vs cca 60% in the placebo and guselkumab arms, respectively.

Results on most of the main secondary endpoints support efficacy. Significantly higher improvement was shown with all endpoints relevant for signs and symptoms of PsA, such as ACR50, ACR70 response rates or DAS28 change from baseline. Secondary endpoints for psoriatic skin disease such as PASI and IGA 0-1 responder rates, and health-related general measures, as HQI-DI, SF-36 PCS and FACIT-fatigue scores have been met. Effect on skin manifestations was somewhat smaller but overall robust and similar to the efficacy observed in the guselkumab psoriasis studies. However, efficacy seems to increase over time.

For soft tissue inflammation, such as dactylitis or enthesitis some slight inconsistencies can be observed. Improvement for these endpoints was mostly significant vs. placebo, however, in study PSA3001, the improvement of dactylitis was not significant with either guselkumab dose regimens vs. placebo. The q8w dose regimen was not significantly better than placebo in study PSA3002. The same was observed for enthesitis in PSA3002, although a pronounced numerical difference in enthesitis resolution was observed in both guselkumab groups compared to placebo. In the CHMP's view, these observations do not impair the overall favourable efficacy of guselkumab in soft tissue manifestations of PsA.

For QoL scores such as HAQ-DI, SF-36 PCS and FACIT Fatigue, both Q8W and Q4W regimens achieved a statistically significant difference at week 24. However, for mental subscale of SF-36 in Study PSA3001, change from baseline was not significant for either guselkumab groups compared to placebo.

According to the prespecified testing hierarchy in study PSA3002, statistical significance of secondary endpoints, which were at lower rank in the testing hierarchy than vdH-SS was not controlled for multiplicity. Therefore, difference between placebo and these secondary endpoints observed for Q8W treatment group were handled as numerical ones which was acceptable to the CHMP.

The proportion of study subject had moderate to severe axial involvement at baseline: 20% and 35% of patients had spondylitis with peripheral arthritis at baseline in studies 3001 and 3002, respectively. This reflects general PsA population, whose 20-50% have involvement of both the spine and peripheral joints, usually with more prominent peripheral joint features-as the EMA Guideline mentions. Among these subjects, a significantly greater reduction from baseline in BASDAI was observed in the guselkumab q8w groups compared with the placebo group in both studies and with q4w dose in study PSA3002; and a numerically greater reduction was observed for the guselkumab q4w group in study PSA3001. At Week 24 in study PSA3001, among subjects with the primary PsA subtype of spondylitis and peripheral arthritis and BASDAI score>0 at baseline, 42% and 35% of subjects in the guselkumab 100 mg q8w and q4w groups, respectively, met the 50% threshold of clinically relevant BASDAI score change, compared to 13% of subjects in the placebo group. In the 23 subjects who were anti-TNFα experienced, all of whom were in study PSA3001, proportions of subjects met the 50% threshold of clinically relevant BASDAI score change were similar. As study 3002 contained a larger sample size of patients with spondylitis the results are considered as significant and clinically relevant. In study PSA3002, 39% and 37% of subjects in the guselkumab q8w and q4w groups, respectively, met the threshold at Week 24, compared to 22% of subjects in the placebo group. In both the individual and pooled studies, greater proportions of subjects

in the guselkumab groups achieved the clinically meaningful improvement in BASDAI of ≥2 points from baseline compared with the placebo group. The results of the analyses described above appear to be consistent and seem to support the hypothesis that guselkumab 100 mg q8w or q4w improves the symptoms of spondylitis in subjects with spondylitis and peripheral arthritis as their primary presentation of PsA.

Greater improvement was consistently observed in the guselkumab group compared with the placebo group across different subgroups, with the exception of a few subgroups in which a small sample size limited the interpretation. Improvement in ACR 20 response at Week 24 was consistently observed in both subgroups with or without concomitant PsA medications including non-biologic DMARDs (eg, MTX), oral corticosteroids, and NSAIDs. Prior exposure to anti-TNFα therapies did not have an impact on ACR 20 and ACR50 response rates and HAQ-DI improvement. Subgroup of patients with prior inadequate response to TNFα-i showed similar efficacy than the overall study population. Efficacy was consistent regardless of baseline MTX (or other DMARD) use (yes/no). The vast majority of subjects who received concomitant cDMARD, received actually MTX 58.4%) and the minority other DMARDs (9.4%). Those data are supportive of the claimed indication.

Guselkumab treatment led to an onset of clinical responses as early as 4 weeks after initiating treatment, with clinically significant improvements through 24 weeks of treatment as assessed by ACR responses and IGA for both the q8w and q4w dose regimens. A similar trend was observed for the change from baseline in DAS28 (CRP) and the change from baseline in HAQ-DI. While lower threshold responses (e.g., ACR 20) usually reached a plateau effect around week 16-week 20 (in PSA3001) or Week 24 (in PSA3002); higher threshold responses (e.g., ACR 70) continued to increase through Week 24.

In study PSA2001, guselkumab demonstrated efficacy compared to placebo in subjects with active PsA across all efficacy endpoints on joint signs and symptoms, enthesitis, dactylitis, physical function, skin disease, and health-related quality of life. Efficacy of guselkumab in the treatment of PsA was maintained through Week 56 of the study. Longer term efficacy of guselkumab in PsA beyond 24 weeks will become available as study PSA3002 is still ongoing, through 112 Weeks, respectively. However, assessed comprehensively in a longer-term data from Phase 3 studies were provided to support maintenance of efficacy over time. Data for joint disease activity and some measures for psoriatic skin disease were provided. These data suggest that efficacy on joint disease activity, radiographic endpoints and on skin disease was maintained and even improved further beyond 24 weeks with both q4w and q8w dose regimens. Long-term data will be assessed comprehensively in a separate variation once also the final CSRs of studyPSA3002 will be available.

Studies PSA3001 and PSA3002 were designed to study the efficacy of guselkumab 100 mg s.c. with either q4w or q8w maintenance dosing and therefore do not allow for an assessment of response after discontinuation from therapy. The MAH explains that guselkumab q8w dose regimen maintained PASI responses and IGA scores through Week 156 in the ongoing long-term extension of psoriasis studies. Supportive data from the randomized withdrawal phase of a large Phase 3 psoriasis study (PSO3002) demonstrated that subjects receiving q8w maintenance therapy generally maintained response while subjects randomized to withdrawal from therapy lost response over time. To date, no signal for decrease in efficacy over time has be observed with guselkumab. No further data on PsA-related endpoints in the subset of psoriatic patients with PsA involvement in long-term extension psoriasis studies are available.

With regards to the lack of active control arm in PsA studies, the MAH refers to psoriasis studies which involved psoriatic patients with PsA, as well. In pivotal PSO studies PSO3001 and 3002 guselkumab was found superior to adalimumab,in Study 3009 (ECLIPSE), guselkumab was superior to secukinumab and in study PSO3003 (NAVIGATE) guselkumab was superior to ustekinumab on psoriasis skin disease-related endpoints also in subgroup of patients with (earlier) PsA diagnosis. Moreover, according to the results of a network meta-analysis for PsA clinical trials both guselkumab Q4W and Q8W dosing regimens were

favourable over or at least comparable to several bDMARDS (including TNFi –s and IL-17 and or IL-23i-s) and tofacitinib in ACR20 response rates.

The incidence rates of antibody formation to guselkumab were small: 4.7%, 2.0% and 2.0% in studies PSA2001, 3001 and 3002, respectively. For subjects who were positive for antibodies to guselkumab, the presence of antibodies to guselkumab had no apparent impact on ACR 20 or ACR 50 in PSA2001 and 3001. However, ACR 20 response rate was lower for subjects who were ADA- positive for ADA (55.6% (n=5) compared with 64.7% of subjects who were ADA- negative. Similarly, ACR 50 response rate was lower for ADA-positives than for ADA-negatives (22.2% (n=2) vs. 32.8%, respectively). In study 3001 through Week 52, the incidence of antibodies to guselkumab was 3.2% (4/126 subjects) in the guselkumab 100 mg q8w group, 7.0% (9/128 subjects) in the guselkumab 100 mg q4w group, and 6.2% (7/113 subjects) in the placebo→100 mg q4w group. In study 3002 through Week 52, the incidence of antibodies to guselkumab was 5.7% (14/247 subjects) in the guselkumab 100 mg q8w group, 3.3% (8/243 subjects) in the guselkumab 100 mg q4w group, and 3.0% (7/237 subjects) in the placebo→100 mg q4w group. The CHMP concluded that while the presence of antibodies to guselkumab did not seem to impact on ACR 20 or ACR 50 responses, the numbers are too low to be conclusive. Therefore, this issue will be further monitored for in the post marketing setting.

For signs and symptoms of PsA, the cumulative evidence did not suggest a clear dose difference in clinical efficacy between the guselkumab 100 mg q8w and q4w dose regimens. Both Q8W and Q4W regimens achieved significantly better results vs placebo for boths in DAS28 (CRP) LDA or remission at weeks 24 and 52. Numerically higher responses and maintenance of both LDA and remission are noted for the Q4W regimen. In the overall study population, dose response was not supported by exposure-response analyses. In PD endpoints, no difference can be seen between the q4w and q8w regimens' PD effects.

In the overall PsA study population, the effect of q4w dose on inhibiton of radiographic progression was higher (and significant) than with q8w dose (non significant) at week 24. The effect of the guselkumab q8w dose regimen on inhibition of radiographic progression was higher than with q4w dose beyond Week 24 (to week 52), suggesting that the benefit of q8w dosing on radiographic endpoints increases with longer exposure. Thus, altogether, the mean change in total mvdH-S was similar in the guselkumab q4w (1.07) and q8w groups (0.97) over 1 year of treatment in the overall PsA study population.

The MAH argues that due to the imbalance across q8w and q4w groups in radiographic score at baseline (with higher BL scores in in q4w group), the benefit of guselkumab q4w may have been underestimated at both Week 24 compared to placebo and at Week 52 compared to guselkumab q8w dose regimen.

The proportions of subjects showing no progression (change of ≤0 from baseline in modified vdH-S scores) based on the vdH-S scores were 63.5% and 67.3% in the guselkumab q8w and q4w groups compared with 64.7% in the placebo group (nominal p=0.752 and p=0.558, respectively) at week 24. The MAH proposed more frequent posology (100 mg s.c. every 4 weeks) for patients at high risk for joint damage according to clinical judgement. To support it, a subgroup whom a more frequent posology can be more appropriate was identified post hoc, based on study PSA3002 results. In this study, structural damage progression was measured radiographically and expressed as the mean change from baseline in the total modified van der Heijde-Sharp (vdH-S) scores. To define PsA patient subgroups who may or may not have a high risk for radiographic progression and may benefit from the q4w dosing regimen the MAH provided post-hoc analyses by relevant baseline disease characteristics which predict risk for radiographic progression in PsA, by baseline radiographic scores and performed risk factor identification via CART analysis. Radiographic results from three separate approaches all supported an incremental benefit of the guselkumab q4w dose regimen on inhibition of structural damage compared to the q8w regimen. The interpretation of additional analyses to identify patients at high risk of radiographic progression is supported by the data presented and it is in line somewhat with EULAR guidelines; however, these guidelines are for patients to commence on csDMARDS and not patients for biological

therapies. The initiation of a biological therapy is recommended in patients not being controlled on a cs DMARD but the CHMP agreed that the same poor prognostic feature should also apply in patients failing cs DMARDS and they can be identified by the treating rheumatologists. In the CHMP's opinion, the MAH has provided sufficient evidence to support the Q4W regimen in patients at high risk for joint damage according to clinical judgement. It is agreed that in some patients' a deeper suppression of the disease activity is needed as well as a need to be controlled as soon as possible, which would not be sufficient with Q8W regimen.

The CHMP asked the MAH to further discuss which parameters should be considered for characterisation of a patient subgroup for whom the q4w dose regimen is more appropriate. The MAH clarified that EULAR, GRAPPA and ACR stresses the importance of individual treatment approach. Specific cut-offs are generally not specified in PsA treatment guidelines but the importance of elevated CRP and the presence of structural damage as evidence of severe disease for treatment considerations are noted. For example, ACR states that "*Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA*". This can be agreed. In addition, using of some of the factors are not feasible in everyday clinical practice for patient selection. At the CHMP's request, Section 5.1 of the SmPC was updated to provide details on the subset of subjects who would benefit most from q4w dose regimen to inhibit radiographic progression. This update was accepted by the CHMP..

2.4.4. Conclusions on the clinical efficacy

The totality of the data provided show that the guselkumab 100 mg s.c. q8w and q4w dose regimens showed benefits over placebo for the treatment of the 3 major manifestations of psoriatic disease (joint, soft tissue and skin), and provided improvement of physical function and health-related quality of life in adults with active psoriatic arthritis. Therefore the claimed indication is considered acceptable by the CHMP. Based on the totality of the efficacy data and analysis, the recommended guselkumab posology for PsA can be the same as approved for the treatment of psoriasis, i.e. 100 mg s.c. q8w after subcutaneous injection at weeks 0 and 4. The MAH proposed a dose regimen q4w for a subgroup of patients at high risk for joint damage defined post-hoc. The MAH has provided a sound rationale for the Q4W maintenance regimen for patients at high risk for joint damage according to clinical judgement and appropriate information was added in 5.1 of the SmPC for the attention of the prescriber i.e. that (in In DISCOVER 2) the observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (i.e., statistical significant difference in mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in subjects with both an elevated C-reactive protein value and high number of joints with erosions at baseline.

2.5. Clinical safety

Introduction

Guselkumab has received marketing approval in the United States, the European Union, and other countries worldwide for the treatment of adult patients with moderate to severe plaque psoriasis and has been marketed since 13 July 2017. The overall safety profile of guselkumab was in line with compounds in the similar therapeutic class interfering with the IL-pathway in psoriasis. In general, the incidence of adverse events was low. The long-term extension data from the Phase 3 psoriasis studies through 3 years

demonstrated that the 3-year safety profile was consistent with the 1-year safety data reported in the original psoriasis marketing application.

The clinical development program of guselkumab for the treatment of active psoriatic arthritis (PsA) includes a completed global Phase 2 study (PSA2001) and 2 global Phase 3 studies (PSA3001 and PSA3002 (ongoing)).

Safety data from all subjects treated in the two global Phase 3 PsA studies, PSA3001 and PSA3002, were pooled and served as the primary analysis set for safety in this submission. Key presentations include safety data from the pooled Phase 3 PsA studies through the placebo-controlled period (Week 24) and through the safety data cutoff of 01 May 2019. Data from the Phase 2 study, PSA2001 were not pooled due to differences in dose regimens and study designs.

Safety assessments included adverse events (AEs; including injection site and allergic reactions), clinical laboratory tests, physical examinations, vital signs, suicidal ideation or behavior (SIB; using the electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]), electrocardiogram (ECG; Week 0 only) findings, concomitant medication review, and early detection of tuberculosis.

To determine if the safety profile of guselkumab in subjects with PsA is comparable with the safety profile for guselkumab in subjects with psoriasis, AEs and clinical laboratory data through the placebo-controlled period for the pivotal Phase 3 studies in psoriasis (PSO3001 and PSO3002) were assessed alongside those from the pooled Phase 3 studies in PsA (PSA3001 and PSA3002) through the common placebo-controlled period (ie, Week 16) across all four studies and through the entire placebo-controlled period (ie, Week 24) for the Phase 3 PsA studies.

Patient exposure

Through the data cut (01 May 2019), a total of 1,229 subjects with active PsA were exposed to guselkumab across the Phase 2 (PSA2001) and Phase 3 PsA studies (PSA3001 and PSA3002), including 1,093 (88.9%) subjects treated for at least 6 months and 588 (47.8%) subjects treated for at least 1 year.

In the Phase 2 PsA (PSA2001) safety analysis set, 129 subjects with active PsA were exposed to guselkumab, including 115 (89.1%) subjects treated for at least 6 months (87 and 28 subjects in the guselkumab q8w and placebo →guselkumab q8w groups, respectively), and 70 (54.3%) subjects treated for at least 1 year.

In the pooled Phase 3 PsA (PSA3001 and PSA3002) safety analysis set, through the data cut, 1,100 subjects with active PsA were exposed to guselkumab, including 978 (88.9%) subjects treated for at least 6 months (364 and 614 subjects in the guselkumab q8w and q4w combined groups, respectively), and 518 (47.1%) subjects treated for at least 1 year (253 and 265 subjects in the guselkumab q8w and q4w combined groups, respectively). Through the data cut, 67.5% (253 of the 375) of subjects randomized to guselkumab q8w and 63.0% (235 of 373) of subjects randomized to guselkumab q4w were treated for at least 1 year.

Through Week 16, in PSO3001 and PSO3002, a total of 823 subjects with psoriasis were exposed to guselkumab.

Through Week 24, in the pooled Phase 3 PsA studies, 42 (3.8%) subjects discontinued study agent, including 12 (3.2%) subjects in the guselkumab 100 mg q8w group, 12 (3.2%) subjects in the guselkumab 100 mg q4w group, and 18 (4.8%) subjects in the placebo group. The most common reasons for discontinuation of study agent were AEs (1.6% [n=18]) and lack of efficacy (0.9% [n=10]).

For PSA3001 through the data cut, 30 (7.9%) subjects discontinued study agent, including 9 (7.1%) subjects in the guselkumab 100 mg q8w group, 4 (3.1%) subjects in the guselkumab 100 mg q4w group, 5 (4.4%) subjects in the placebo→guselkumab 100 mg q4w group, and 12 (9.5%) subjects in the placebo group. The most common reasons for discontinuation of study agent were lack of efficacy (2.9% [n=11]) followed by AEs (2.4% [n=9]).

For PSA3002 through the data cut, 51 (6.9%) subjects discontinued study agent, including 15 (6.0%) subjects in the guselkumab 100 mg q8w group, 18 (7.3%) subjects in the guselkumab 100 mg q4w group, 10 (4.2%) subjects in the placebo→guselkumab 100 mg q4w group, and 8 (3.3%) subjects in the placebo group. The most common reasons for discontinuation of study agent were AEs (2.6% [n=19]) and lack of efficacy (2.6% [n=19]).

Through the data cut in the pooled Phase 3 PsA studies, 81 (7.2%) subjects discontinued study agent, including 24 (6.4%) subjects in the guselkumab 100 mg q8w group, 22 (5.9%) subjects in the guselkumab 100 mg q4w group, 15 (4.3%) subjects in the placebo→guselkumab 100 mg q4w group, and 20 (5.4%) subjects in the placebo group. The most common reasons for discontinuation of study agent were lack of efficacy (2.7% [n=30]) followed by AEs (2.5% [n=28]).

The proportion of treated subjects in the pooled Phase 3 PsA studies who had prior exposure to PsA medications was generally similar across all treatment groups. All subjects had prior exposure to medication and/or therapy for PsA and 91.1% had prior treatment with non-biologic DMARDs, immunosuppressives or apremilast; the majority of subjects received 1 treatment (59.8%) followed by 2 treatments (23.9%), and ≥3 treatments (7.3%).

The proportions of treated subjects in the pooled Phase 3 PsA studies who received non-biologic DMARDs, oral corticosteroids for PsA, or NSAIDs for PsA at baseline were well balanced across treatment groups. Among subjects receiving non-biologic DMARDs at baseline, the majority of subjects were receiving MTX.

Adverse events

Study PSA2001

- The proportions of subjects with 1 or more AEs were comparable between the placebo group and the guselkumab group through Week 16 (28.6% and 27.0%, respectively) and through Week 24 (32.7% and 36.0%, respectively). Through Week 56, the frequency of overall AEs in the guselkumab group did not increase disproportionally (ie, >2-fold) with >2-fold longer exposure of guselkumab compared to Week 24. Through Week 56, 17.2% of subjects in the placebo → guselkumab crossover group, 46.0% of subjects in the guselkumab, and 39.5% in the guselkumab combined group reported 1 or more AEs.

- Adverse events in the Infections and infestations SOC were most frequently reported throughout the study, and the proportions were comparable between the placebo group and the guselkumab group through Week 16 (18.4% and 14.0%, respectively) and through Week 24 (20.4% and 17.0%, respectively). Through Week 56, the frequency of Infections and infestations in the guselkumab group did not increase disproportionally (ie, >2 fold) with >2 fold longer exposure of guselkumab compared to Week 24. Through Week 56, 3.4% in the placebo → guselkumab crossover group, 27.0% of subjects in the guselkumab group, and 21.7% in the guselkumab combined group reported 1 or more AEs in the SOC of Infections and infestations.

- The most common AE in both treatment groups was nasopharyngitis which was reported in 10.2% of the subjects in the placebo group and 6.0% in the guselkumab group through Week 24, and 0 in the placebo → guselkumab crossover group, 10.0% in the guselkumab group, and 7.8% in the guselkumab combined group through Week 56. Other AEs reported in >2% in the guselkumab combined

group through Week 56 included ALT increased (4.7%), leukopenia (4.7%), AST increased (3.9%), neutropenia (3.1%), upper respiratory tract infection (URTI, 3.1%), and hepatic steatosis (2.3%).

- The concomitant use of MTX with guselkumab did not appear to have a large impact on the overall frequency of AEs or AE profiles through Weeks 16, 24, and 56.

Infections

- The proportions of subjects who reported 1 or more infections (as assessed by the investigators) were comparable between the placebo group and the guselkumab group through Week 16 (18.4% and 13.0%, respectively) and through Week 24 (20.4% and 16.0%, respectively). Through Week 56, the frequency of overall infections in the guselkumab group did not increase disproportionally (ie, >2-fold) with >2-fold longer exposure of guselkumab compared to Week 24. Through Week 56, 3.4% in the placebo → guselkumab crossover group, 26.0% of subjects in the guselkumab, and 20.9% in the guselkumab combined group reported 1 or more infections.
- Through Week 56, 1 (0.8%) subject in the guselkumab combined group reported serious infections of pneumonia.
- No cases of TB or opportunistic infections were reported through Week 56.

Malignancies

- Through Week 56, 1 case of basal cell carcinoma was reported by 1 (0.8%) subject in the guselkumab combined group.

Cardiovascular Events

- Through Week 56, 1 MACE (MI) was reported by 1 (0.8%) subject in the guselkumab combined group.

Anaphylactic or Serum Sickness-like Reactions

- No cases of anaphylactic or serum sickness-like reactions were reported in the study through Week 56.

Injection-site Reactions

- Through Week 44, there was no ISR reported in the guselkumab group.

Pooled Phase 3 Psoriatic Arthritis Studies

Through Week 24, the average duration of follow-up and the frequency of key safety events in the pooled Phase 3 PsA studies was similar across the guselkumab 100 mg q8w, guselkumab 100 mg q4w, and placebo groups except for ISRs which were more common in the guselkumab groups. In addition, the number of subjects with AEs, serious AEs, AEs leading to discontinuation of study agent, infections, and serious infections per 100 subject-years of follow-up in the guselkumab groups were generally comparable with the placebo group.

Table 1: Overall Summary of Treatment-emergent Adverse Events Through the Placebo-Controlled Period – Week 24; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Placebo-Controlled Period Through Week 24[a]			
		Guselkumab		
	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	372	375	373	748
Avg duration of follow up (weeks)	24.2	24.1	24.1	24.1
Avg number of study agent admins	5.9	5.9	5.9	5.9
Avg number of placebo admins	5.9	2.0	0.0	1.0
Avg number of guselkumab admins	-	3.9	5.9	4.9
Subjects with 1 or more AEs	176 (47.3%)	182 (48.5%)	182 (48.8%)	364 (48.7%)
Subjects with 1 or more serious AEs	12 (3.2%)	7 (1.9%)	8 (2.1%)	15 (2.0%)
Subjects with 1 or more AEs leading to discontinuation of study agent	7 (1.9%)	5 (1.3%)	8 (2.1%)	13 (1.7%)
Subjects with 1 or more AEs with severe intensity	6 (1.6%)	3 (0.8%)	2 (0.5%)	5 (0.7%)
Subjects with 1 or more infections	77 (20.7%)	73 (19.5%)	80 (21.4%)	153 (20.5%)
Subjects with 1 or more serious infections	3 (0.8%)	1 (0.3%)	3 (0.8%)	4 (0.5%)
Subjects with 1 or more injection site reactions	1 (0.3%)	5 (1.3%)	4 (1.1%)	9 (1.2%)
Subjects with 1 or more events of malignancy	1 (0.3%)	2 (0.5%)	0	2 (0.3%)
Subjects with 1 or more opportunistic infections	0	0	0	0
Subjects with 1 or more anaphylactic reactions or serum sickness reactions	0	0	0	0
Subjects with 1 or more events leading to death	2 (0.5%)	0	0	0

AE=adverse events', q4w=every 4 weeks; q8w=every 8 weeks

Note: Adverse events are coded using MedDRA Version 21.1. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

[a]: For subjects in all treatment groups who discontinued study treatment early with the last study treatment (placebo or guselkumab) administrated prior to Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.

[b]: For subjects in placebo group who changed treatment from placebo to guselkumab due to cross-over or inadvertently, only data prior to first administration of guselkumab were included in this group. Data on and after the first administration of guselkumab were not included in this group.

Adapted from: [TSFAE01S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFAE01S12.SAS] 17JUN2019, 17:13

Through the data cut (01 May 2019), the overall safety profile of guselkumab in the pooled Phase 3 PsA studies was similar to the overall safety profile through Week 24 and the overall safety profiles of the guselkumab q8w and q4w groups were similar to each other.

TSFAE09S12: Number of Subjects with 1 or More Treatment-Emergent Adverse Events per Hundred Subject-Years of Follow-Up Through Data Cut; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Placebo Controlled Period through Week 24[a]				Reporting Period through Data Cut				
	Guselkumab				Guselkumab				
	Placebo[b]	100 mg q8w	100 mg q4w	Combined	100 mg q8w	100 mg q4w	Placebo → 100 mg q4w[c]	100 mg q4w Combined[c]	All Combined[c]
Analysis set: Safety Analysis Set	372	375	373	748	375	373	352	725	1100
Total subject-years of follow-up	173	173	172	346	373	371	193	564	937
Median subject-years of follow-up	0.5	0.5	0.5	0.5	1.0	1.0	0.5	0.8	0.8
All Adverse Events									
Total subject-years of follow-up[e]	123	123	119	242	207	209	148	357	563
Number of subjects with AEs per hundred subject-years of follow-up (95% CI)[d,e]	142.81 (122.49, 165.54)	147.65 (126.98, 170.73)	152.89 (131.49, 176.79)	150.23 (135.19, 166.48)	117.62 (103.29, 133.37)	114.34 (100.31, 129.80)	90.00 (75.36, 106.67)	104.26 (93.94, 115.42)	109.16 (100.70, 118.14)
Serious Adverse Events									
Total subject-years of follow-up[e]	170	171	170	341	364	364	189	552	917
Number of subjects with serious AEs per hundred subject-years of follow-up (95% CI)[d,e]	7.06 (3.65, 12.33)	4.09 (1.64, 8.42)	4.70 (2.03, 9.27)	4.39 (2.46, 7.25)	5.49 (3.35, 8.48)	4.95 (2.93, 7.82)	7.42 (4.06, 12.45)	5.79 (3.96, 8.18)	5.67 (4.24, 7.44)
Adverse Events Leadig to Discontinuation of Study Agent									
Total subject-years of follow-up[e]	171	172	170	342	371	368	192	561	931
Number of subjects with AEs leading to discontinuation of study agent per hundred subject-years of follow-up (95% CI)[d,e]	4.09 (1.64, 8.42)	2.91 (0.95, 6.79)	4.70 (2.03, 9.26)	3.80 (2.02, 6.50)	2.16 (0.93, 4.25)	2.71 (1.30, 4.99)	3.12 (1.15, 6.80)	2.85 (1.63, 4.64)	2.58 (1.65, 3.83)
Infections									
Total subject-years of follow-up[e]	154	157	153	309	301	301	172	473	775
Number of subjects with infections per hundred subject-years of follow-up (95% CI)[d,e]	49.89 (39.37, 62.35)	46.57 (36.50, 58.56)	52.40 (41.55, 65.22)	49.45 (41.92, 57.93)	42.16 (35.14, 50.16)	38.51 (31.82, 46.19)	39.47 (30.65, 50.04)	38.86 (33.45, 44.90)	40.14 (35.80, 44.86)
Serious Infections									
Total subject-years of follow-up[e]	172	173	172	345	371	370	192	562	933
Number of subjects with serious infections per hundred subject-years of follow-up (95% CI)[d,e]	1.74 (0.36, 5.09)	0.58 (0.01, 3.22)	1.75 (0.36, 5.11)	1.16 (0.32, 2.97)	1.35 (0.44, 3.14)	1.08 (0.29, 2.77)	2.61 (0.85, 6.08)	1.60 (0.73, 3.04)	1.50 (0.82, 2.52)

Note: Adverse events are coded using MedDRA Version 21.1.
[a]: For subjects in all treatment groups who discontinued study treatment early with the last study treatment (placebo or guselkumab) administrated prior to Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.
[b]: For subjects in placebo group who changed treatment from placebo to guselkumab due to cross-over or inadvertently, only data prior to first administration of guselkumab were included in this group. Data on and after the first administration of Guselkumab were not included in this group.
[c]: For subjects in placebo group who changed treatment from placebo to guselkumab due to cross-over or inadvertently, only data on and after first administration of guselkumab were included in this group. Data prior to the first administration of Guselkumab were not included in this group.
[d]: Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.
[e]: For number of subjects with the said events, subjects are counted only once for the said event, regardless of the number of times they actually experienced the event and duration of follow-up is only through the occurrence of the first said event.

Any Adverse Events

The proportions of subjects reporting 1 or more AEs through Week 24 were similar in the guselkumab 100 mg q8w, guselkumab 100 mg q4w, and placebo groups: 48.5%, 48.8%, and 47.3%, respectively. Infections and infestations was the SOC with the highest proportion of reported AEs in the guselkumab q8w (19.5%) and q4w (19.3%) groups, and the proportion was comparable in the placebo (19.9%) group. Other SOCs in which the proportions of subjects with AEs in either the guselkumab q8w or q4w groups were >10% were Investigations (q8w [13.6%], q4w [11.5%], and placebo [7.0%]) and Musculoskeletal and connective tissue disorders (q8w [9.9%], q4w [10.2%], and placebo [12.6%]).

- The most frequently reported AEs in subjects treated with guselkumab were ALT increased, nasopharyngitis, AST increased, and URTI.
  - Alanine aminotransferase increased was reported in 6.1%, 7.5%, and 3.8% of subjects in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.
  - Nasopharyngitis was reported in 6.9%, 5.1%, and 4.6% of subjects in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.
  - Aspartate aminotransferase increased was reported in 6.1%, 3.8%, and 2.4% of subjects in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.

  - Upper respiratory tract infection was reported in 3.5%, 6.2%, and 4.6% of subjects in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.

- For most AEs, the frequencies of AEs were comparable in the guselkumab q8w, guselkumab q4w, and placebo groups. The most frequently reported AEs in subjects treated with guselkumab were alanine aminotransferase (ALT) increased, nasopharyngitis, aspartate aminotransferase (AST) increased, and upper respiratory tract infection (URTI). The following AEs were reported more frequently in the guselkumab groups compared with the placebo group (ie, in ≥1% of subjects in any guselkumab group and ≥2 times more frequently in the guselkumab combined group compared with the placebo group): AST increased, bronchitis, headache, respiratory tract infection, injection site erythema and oropharyngeal pain. Headache and injection site erythema were previously identified as ADRs and respiratory tract infection, bronchitis, and transaminases increased were identified as new ADRs for guselkumab. Upon further review, oropharyngeal pain is not considered a new ADR for guselkumab.
- The following AEs were reported more frequently in the guselkumab q4w group compared with the q8w group (ie, in ≥1% of subjects in any guselkumab group and ≥2 times more frequently in the guselkumab q4w group compared with the guselkumab q8w group): neutrophil count decreased, hyperuricaemia, and hepatic steatosis. Neutrophil count decreased was identified as a new ADR for guselkumab. Upon further review, hyperuricaemia and hepatic steatosis are not considered new ADRs for guselkumab.

Table 1: Number of Subjects with 1 or More Treatment-Emergent Adverse Events in at Least 1% in Any Treatment Group Through Week 24 by MedDRA Preferred Term; Treated Subjects (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Placebo-Controlled Period through Week 24[a]			
		Guselkumab		
	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	372	375	373	748
Avg duration of follow-up (weeks)	24.2	24.1	24.1	24.1
Avg number of study agent admins	5.9	5.9	5.9	5.9
Subjects with 1 or more AEs	176 (47.3%)	182 (48.5%)	182 (48.8%)	364 (48.7%)
Preferred term				
Nasopharyngitis	17 (4.6%)	26 (6.9%)	19 (5.1%)	45 (6.0%)
Alanine aminotransferase increased	14 (3.8%)	23 (6.1%)	28 (7.5%)	51 (6.8%)
Upper respiratory tract infection	17 (4.6%)	13 (3.5%)	23 (6.2%)	36 (4.8%)
Aspartate aminotransferase increased	9 (2.4%)	23 (6.1%)	14 (3.8%)	37 (4.9%)
Bronchitis	4 (1.1%)	6 (1.6%)	11 (2.9%)	17 (2.3%)
Enthesopathy	13 (3.5%)	11 (2.9%)	13 (3.5%)	24 (3.2%)
Hypertension	6 (1.6%)	6 (1.6%)	4 (1.1%)	10 (1.3%)
Headache	3 (0.8%)	8 (2.1%)	7 (1.9%)	15 (2.0%)
Neutropenia	3 (0.8%)	6 (1.6%)	1 (0.3%)	7 (0.9%)
Viral upper respiratory tract infection	4 (1.1%)	3 (0.8%)	4 (1.1%)	7 (0.9%)
Hyperglycaemia	4 (1.1%)	5 (1.3%)	3 (0.8%)	8 (1.1%)
Leukopenia	2 (0.5%)	6 (1.6%)	1 (0.3%)	7 (0.9%)
Dactylitis	12 (3.2%)	7 (1.9%)	7 (1.9%)	14 (1.9%)
Psoriatic arthropathy	11 (3.0%)	4 (1.1%)	0	4 (0.5%)
Diarrhoea	3 (0.8%)	6 (1.6%)	4 (1.1%)	10 (1.3%)
Anaemia	7 (1.9%)	7 (1.9%)	3 (0.8%)	10 (1.3%)
Arthralgia	6 (1.6%)	3 (0.8%)	3 (0.8%)	6 (0.8%)
Injection site erythema	0	5 (1.3%)	2 (0.5%)	7 (0.9%)
Hyperuricaemia	0	0	5 (1.3%)	5 (0.7%)
Pharyngitis	4 (1.1%)	4 (1.1%)	1 (0.3%)	5 (0.7%)
Oropharyngeal pain	1 (0.3%)	4 (1.1%)	2 (0.5%)	6 (0.8%)
Urinary tract infection	1 (0.3%)	4 (1.1%)	0	4 (0.5%)
Nausea	3 (0.8%)	3 (0.8%)	5 (1.3%)	8 (1.1%)
Neutrophil count decreased	0	1 (0.3%)	6 (1.6%)	7 (0.9%)
Pyrexia	2 (0.5%)	5 (1.3%)	0	5 (0.7%)
Respiratory tract infection	1 (0.3%)	5 (1.3%)	4 (1.1%)	9 (1.2%)
Hepatic steatosis	2 (0.5%)	0	4 (1.1%)	4 (0.5%)
Psoriasis	12 (3.2%)	1 (0.3%)	0	1 (0.1%)
Lymphopenia	4 (1.1%)	3 (0.8%)	0	3 (0.4%)
Abdominal pain upper	4 (1.1%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Weight increased	1 (0.3%)	4 (1.1%)	0	4 (0.5%)

AE=adverse events; q4w=every 4 weeks; q8w=every 8 weeks

Note: Adverse events are coded using MedDRA Version 21.1. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

[a]: For subjects in all treatment groups who discontinued study treatment early with the last study treatment (placebo or guselkumab) administrated prior to Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.

[b]: For subjects in placebo group who changed treatment from placebo to guselkumab due to cross-over or inadvertently, only data prior to first administration of guselkumab were included in this group. Data on and after the first administration of guselkumab were not included in this group.

Adapted from: [TSFAE05S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFAE05S12.SAS] 17JUN2019, 17:14

Through Week 24, the majority of AEs were of mild intensity (61.0%, 65.4%, and 55.1% of AEs reported in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively). The number of subjects reporting 1 or more AEs of severe intensity was low: 3 (0.8%) subjects in the guselkumab q8w group, 2 (0.5%) subjects in the guselkumab q4w group, and 6 (1.6%) subjects in the placebo group.

The safety profile of guselkumab through the data cut is similar to the safety profile of guselkumab through Week 24 and the frequency of individual AEs were generally comparable between the guselkumab q8w and q4w groups.

Through the data cut, the proportions of subjects reporting 1 or more AEs were similar across treatment groups; 64.8% in the guselkumab q8w group and 64.1% in the guselkumab q4w group. Infections and infestations was the SOC with the highest proportion of AEs in the guselkumab q8w (33.1%) and q4w (29.0%) groups. Other SOCs in which the proportions of subjects with AEs in either the guselkumab q8w or q4w groups were >10% were Investigations (q8w [17.1%] and q4w [15.8%]) and Musculoskeletal and connective tissue disorders (q8w [14.7%] and q4w [13.7%]).

- The most frequently reported AEs in subjects treated with guselkumab were nasopharyngitis, ALT increased, URTI, and AST increased.
  - Nasopharyngitis was reported in 10.9% of subjects in the guselkumab q8w group and 8.6% of subjects in the q4w group.
  - Alanine aminotransferase increased was reported in 8.3% of subjects in the guselkumab q8w group and 10.2% of subjects in the q4w group.
  - Upper respiratory tract infection was reported in 7.2% of subjects in the guselkumab q8w group and 7.8% of subjects in the q4w group.
  - Aspartate aminotransferase increased was reported in 7.5% of subjects in the guselkumab q8w group and 6.2% of subjects in the q4w group.

As through Week 24, through the data cut there were no reports of new onset or exacerbation of inflammatory bowel disease, including Crohn's disease and ulcerative colitis in guselkumab-treated subjects.

Through the data cut, the overall AE rates per 100 subject-years of follow-up were 211.92, 179.17, and 175.39, for the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups, respectively. The SOC with the highest AE rates per 100 subject-years of follow-up was Infections and infestations; 55.53, 47.69, and 48.72 for the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups, respectively.

Through the data cut, the proportions of subjects with mild, moderate, or severe AEs, were generally similar in the guselkumab q8w and q4w groups. The number of subjects reporting 1 or more AEs of severe intensity was low: 8 (2.1%) subjects in the guselkumab q8w group and 10 (2.7%) subjects in the guselkumab q4w group.

A greater frequency of decreases in neutrophil counts and WBC counts was observed with longer duration of exposure through 1 year. The proportions of subjects who experienced neutrophil count decreases of CTCAE Grade ≥1 were 12.9% and 11.6% in the guselkumab q8w and every 4 weeks (q4w) groups, respectively, and 10.2% in all guselkumab-treated subjects through 1 year. The proportions of subjects who experienced WBC count decreases of CTCAE Grade ≥1 were 10.5% and 10.3% in the guselkumab q8w and q4w groups, respectively, and 9.2% in all guselkumab-treated subjects through 1 year. No Grade 3 or higher WBC count decrease was observed through 1 year. Grade ≥2 neutrophil count decreases and Grade 2 WBC count decreases in guselkumab-treated subjects were generally not associated with infections. Mean values for neutrophil counts and WBC counts in the guselkumab q8w and q4w groups did not further decrease from Week 24 through 1 year of treatment.

Through 1 year, most post-baseline increases in ALT and AST were Grade 1 and the proportions of subjects with Grade 1 or higher post-baseline increases in ALT were higher in the guselkumab q4w (46.9%) group compared with the q8w group (36.2%). The proportions of subjects with Grade 1 or

higher post-baseline increases in AST were also slightly higher in the guselkumab q4w (33.2%) group compared with the q8w group (26.3%). A greater frequency was observed with the longer duration of exposure through 1 year.

AEs reported in the Hepatobiliary disorders SOC were comparable between the guselkumab q4w (3.5%) and q8w (2.7%) groups. The majority of AEs reported through 1 year were preferred terms (PTs) related to hepatic steatosis for both the q4w (2.7%) and q8w (1.3%) groups. Through 1 year, 3 subjects in the guselkumab q4w group reported PTs of Drug-induced liver injury (DILI), Hepatitis toxic, and Hepatocellular injury (one subject each) and causality was assessed as related to the concomitant anti-TB therapy in all 3 subjects.

There were no events that satisfied the criteria for Hy's Law in guselkumab-treated subjects through 1 year.

In subjects with baseline MTX use, Grade 1 or higher increases in ALT were more frequent than in subjects without baseline MTX use.

A review of all postmarketing events reported with laboratory test results and/or with PTs relevant for liver injury did not identify any event of potential DILI attributed to guselkumab.

Infections

Through Week 24, the proportion of subjects reporting at least 1 AE categorized as an infection by the investigator was 19.5% in the guselkumab 100 mg q8w group, 21.4% in the guselkumab 100 mg q4w group, and 20.7% in the placebo group.

The most frequently reported AEs of infection through Week 24 were nasopharyngitis (6.9%, 5.1%, and 4.6% in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively), URTI (3.5%, 6.2%, and 4.6% in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively), and bronchitis (1.6%, 2.9%, and 1.1% in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively). All other infections were reported in <2% of subjects in both of the guselkumab groups.

Serious infections were reported in 1 subject in the guselkumab q8w group (pyrexia), 3 subjects in the guselkumab q4w group (acute hepatitis B, oophoritis, and pneumonia influenzal), and 3 subjects in the placebo group (pustular psoriasis, pneumonia bacterial, and URTI were reported in 1 subject, abscess limb infection was reported in 1 subject, and post-procedural fistula was reported in 1 subject). There was no increased risk of a serious infection in the guselkumab q8w, q4w, or combined (q8w and q4w) groups compared with the placebo group or in the guselkumab q4w group compared with the guselkumab q8w group.

Through Week 24, the overall AEs of infection rates per 100 subject-years of follow-up were 58.27, 62.71, and 58.48, for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively. Through Week 24, the overall AEs of serious infections rates per 100 subject-years of follow-up were 0.58, 1.74, and 4.05 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.

Through the data cut, AEs of infections were reported at a frequency of 33.9% in the guselkumab 100 mg q8w group and 31.1% in the guselkumab 100 mg q4w group. The most frequently reported AEs of infection through the data cut were nasopharyngitis (10.9% and 8.6% in the guselkumab q8w and q4w groups, respectively), URTI (7.2% and 7.8% in the guselkumab q8w and q4w groups, respectively), bronchitis (4.0% and 4.3% in the guselkumab q8w and q4w groups, respectively), and viral URTI (2.4% and 1.3% in the guselkumab q8w and q4w groups, respectively). All other infections were reported in <2% of subjects in both of the guselkumab groups.

Through the data cut, the overall AE of infection rates per 100 subject-years of follow-up were 57.94, 52.81, 53.15 for the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups. Through

the data cut, the overall AEs of serious infections rates per 100 subject-years of follow-up were 1.61, 1.08, and 1.77 for the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups, respectively.

No cases of active TB, opportunistic infections, or candida infections were reported through the data cut in PSA3001 and PSA3002.

Injection-site Reactions

Through Week 24, the number of subjects that reported 1 or more ISRs was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) subjects in the guselkumab q8w group, 4 (1.1%) subjects in the guselkumab q4w group, and 1 (0.3%) subject in the placebo group. The most frequently reported ISR was injection site erythema.

Through Week 24, there were no serious ISRs. All subjects who reported guselkumab ISRs reported ISRs of mild intensity with the exception of 1 subject in the guselkumab q4w group who reported 3 ISRs of moderate intensity. This subject discontinued study agent after the first dose due to injection site erythema, injection site swelling, and injection site warmth.

Through the data cut, the number of subjects that reported 1 or more ISRs was low and generally similar across the treatment groups; 8 (2.1%) subjects in the guselkumab 100 mg q8w group and 11 (2.9%) subjects in the guselkumab 100 mg q4w group. The most frequently reported ISR was injection site erythema.

Through the data cut, there were no serious ISRs. All subjects with guselkumab ISRs reported ISRs of mild intensity with the exception of 3 subjects in the guselkumab q4w group who reported ISRs of moderate intensity. Through the data cut, 2 of these subjects with ISRs of moderate intensity discontinued study agent due to ISRs; 1 subject discontinued study agent prior to Week 24 and an additional subject in the guselkumab group q4w group discontinued study agent after Week 24 and through the data cut, due to 2 ISRs of moderate intensity, injection site erythema and injection site rash.

Malignancies

Through Week 24, malignancies were reported in 2 (0.5%) subjects in the guselkumab 100 mg q8w group (plasma cell myeloma [reported 15 days after the first study agent administration] and malignant melanoma in situ [reported 41 days after the first study agent administration]) and 1 subject in the placebo group (clear cell renal cell carcinoma. In the subject who reported plasma cell myeloma, clinical laboratory analysis of a serum sample collected prior to the first administration of guselkumab indicated an elevated level of gamma globulin and M protein, excess free kappa light chain production, and a marked abnormal kappa/lambda ratio. The subject diagnosed with malignant melanoma in situ had a history of the skin lesion for 1 year prior to biopsy and diagnosis and was receiving MTX at baseline. There were no reports of NMSC.

Through the data cut, in addition to the malignancies described through Week 24, squamous cell carcinoma in situ and malignant melanoma in situ were reported in 1 subject in the placebo→guselkumab 100 mg q4w group. This $\geq$65 year-old subject with a history of actinic keratoses and in situ squamous cell carcinoma 3 months prior to enrollment and a maternal history of 2 lesions of malignant melanoma was diagnosed through biopsy at a routine skin check.

The numbers of subjects reporting malignancies through the data cut were as follows:

- All malignancies:
  - Guselkumab q8w: 0.54/100 subject-years of follow-up (95% CI: 0.07, 1.94)

  - Guselkumab q4w: 0.00/100 subject-years of follow-up (95% CI: 0.00, 0.81)
  - Guselkumab q4w combined: 0.18/100 subject-years of follow-up (95% CI: 0.00, 0.99)
- NMSC:
  - Guselkumab q8w: 0.00/100 subject-years of follow-up (95% CI: 0.00, 0.80)
  - Guselkumab q4w: 0.00/100 subject-years of follow-up (95% CI: 0.00, 0.81)
  - Guselkumab q4w combined: 0.18/100 subject-years of follow-up (95% CI: 0.00, 0.99)
- Malignancies other than NMSC:
  - Guselkumab q8w: 0.54/100 subject-years of follow-up (95% CI: 0.07, 1.94)
  - Guselkumab q4w: 0.00/100 subject-years of follow-up (95% CI: 0.00, 0.81)
  - Guselkumab q4w combined: 0.18/100 subject-years of follow-up (95% CI: 0.00, 0.99)

Major Adverse Cardiovascular Events

Through Week 24 of the pooled Phase 3 PsA studies, 1 MACE (ie, nonfatal ischemic stroke) was reported in a subject in the guselkumab 100 mg q4w group and 1 MACE (ie, fatal cardiac failure) was reported in a subject in the placebo group. There were no additional reports of MACE reported after Week 24 and through the data cut.

Suicidal Ideation and Behaviors

Through Week 24, 4 subjects reported eC-SSRS level 1 suicidal ideation of “wish to be dead”; 1 subject in each of the guselkumab groups and 2 subjects in the placebo group. Through the data cut, an additional 4 subjects (2 subjects in the guselkumab 100 mg q8w group, 1 subject in the guselkumab 100 mg q4w group, and 1 subject in the placebo→guselkumab 100 mg q4w group), reported eC-SSRS level 1 suicidal ideation of “wish to be dead”. There were no abnormal eC-SSRS findings for events of suicidal behavior or self-injurious behavior without suicidal intent. Two of the 6 reports of abnormal eC SSRS scores in guselkumab-treated subjects were also reported as AEs. A history of suicidal ideation was reported before screening for 2 of the 6 guselkumab-treated subjects. A history of depression or other social or economic contributing factors (e.g., loss of employment) was noted in 4 of the 6 guselkumab-treated subjects.

Through Week 24, the number of subjects reporting SIB or self-injurious behavior without suicidal intent was 0.58/100 subject-years of follow-up for both the guselkumab q8w and q4w groups and 1.16/100 subject-years of follow-up for the placebo group. Through the data cut, there was no evidence for an increase in the follow-up adjusted number of subjects reporting SIB over time and the follow-up adjusted number of subjects reporting SIB in both the guselkumab q8w and q4w groups remained lower than the placebo group through Week 24. No subjects discontinued study agent due to SIB.

Table 1: Number of Subjects with 1 or More Treatment-emergent Events of Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent per Hundred Subject-Years of Follow-Up by Worst Severity through Data Cut; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

			Guselkumab		
	100 mg q8w	100 mg q4w	Placebo → 100 mg q4w[a]	100 mg q4w Combined[a]	All Combined[a]
Analysis set: Safety Analysis Set	375	373	352	725	1100
Subjects with 1 or more suicidal ideation or behavior or self-injurious behavior without suicidal intent[b]					
Total subject-years of follow-up	372	370	193	564	935
Median subject-years of follow-up	1.0	1.0	0.5	0.8	0.8
Observed number of subjects	3	2	1	3	6
Incidence (95% CI) per hundred subject-years of follow-up[c]	0.81 (0.17, 2.36)	0.54 (0.07, 1.95)	0.52 (0.01, 2.88)	0.53 (0.11, 1.56)	0.64 (0.24, 1.40)
Subjects with 1 or more suicidal ideation or behavior[b]					
Total subject-years of follow-up	372	370	193	564	935
Median subject-years of follow-up	1.0	1.0	0.5	0.8	0.8
Observed number of subjects	3	2	1	3	6
Incidence (95% CI) per hundred subject-years of follow-up[c]	0.81 (0.17, 2.36)	0.54 (0.07, 1.95)	0.52 (0.01, 2.88)	0.53 (0.11, 1.56)	0.64 (0.24, 1.40)
Subjects with 1 or more suicidal ideation (code=1 – 5)[b]					
Total subject-years of follow-up	372	370	193	564	935
Median subject-years of follow-up	1.0	1.0	0.5	0.8	0.8
Observed number of subjects	3	2	1	3	6
Incidence (95% CI) per hundred subject-years of follow-up[c]	0.81 (0.17, 2.36)	0.54 (0.07, 1.95)	0.52 (0.01, 2.88)	0.53 (0.11, 1.65)	0.64 (0.24, 1.40)
Subjects with 1 or more suicidal behavior (codes=6 – 10)[b]					
Total subject-years of follow-up	373	371	193	564	937
Median subject-years of follow-up	1.0	1.0	0.5	0.8	0.8
Observed number of subjects	0	0	0	0	0
Incidence (95% CI) per hundred subject-years of follow-up[c]	0.00 (0, 0.80)	0.00 (0, 0.81)	0.00 (0, 1.55)	0.00 (0, 0.53)	0.00 (0, 0.32)
Subjects with 1 or more self-injurious behavior without suicidal intent[d]					
Total subject-years of follow-up	373	371	193	564	937
Median subject-years of follow-up	1.0	1.0	0.5	0.8	0.8
Observed number of subjects	0	0	0	0	0
Incidence (95% CI) per hundred subject-years of follow-up[c]	0.00 (0, 0.80)	0.00 (0, 0.81)	0.00 (0, 1.55)	0.00 (0, 0.53)	0.00 (0, 0.32)

CI=confidence interval; q4w=every 4 weeks; q8w=every 8 weeks

[a]: For subjects in placebo group who changed treatment from placebo to guselkumab due to crossover or inadvertently, only data on and after first administration of guselkumab were included in this group. Data prior to the first administration of guselkumab were not included in this group.

[b]: Based on adverse events identified by the investigators as events of suicidal ideation or behavior or eC-SSRS findings > 0.

[c]: Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.

[d]: Based on eC-SSRS data.

Adapted from: [TSFSIB03S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFSIB03S12.SAS] 17JUN2019, 17:36

New-onset or exacerbation of inflammatory bowel disease

Through Week 24, there were no reports of new onset or exacerbation of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, in guselkumab-treated subjects. Long-term data is unavailable.

Anaphylaxis and Serum Sickness Reactions

No cases of anaphylaxis or serum sickness reaction were reported through the data cut in PSA3001 and PSA3002.

Serious adverse event / deaths / other significant events

Study PSA2001

- No deaths occurred in the study through Week 56.

- Through Week 24, 1 (2.0%) subject in the placebo group reported an SAE of joint injury and 1 (1.0%) subject in the guselkumab group reported a SAE of MI. After Week 24, 5 additional SAEs (osteoarthritis, unequal pupils, radius fracture, pneumonia, and ulcerative keratitis) were reported in the guselkumab group. Through Week 56, 6.0% of the guselkumab group (4.7% of the guselkumab combined group) reported 1 or more SAEs. All events were singular in nature and there was no evident pattern observed.

Pooled Phase 3 Psoriatic Arthritis Studies

Deaths

In PSA3001 through Week 24 cardiac failure leading to death on Study Day 166 was reported in a subject in the placebo group who did not receive any guselkumab prior to death. Additionally, through the data cut pneumonia leading to a death was reported in a subject in the placebo group who did not receive any guselkumab. In PSA3002, no deaths were reported.

Other Serious Adverse Events

Through Week 24, SAEs were reported in 7 (1.9%), 8 (2.1%), and 12 (3.2%) subjects in the guselkumab 100 mg q8w, guselkumab 100 mg q4w, and placebo groups, respectively. There was no increased risk of a SAE in the guselkumab q8w, q4w, or combined groups compared with the placebo group or in the guselkumab q4w group compared with the guselkumab q8w group.

- Infections and infestations was the SOC in which the highest proportions of subjects reported SAEs; 0, 3 (0.8%), and 2 (0.5%) subjects in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.

- All individual SAEs were reported in single subjects treated with guselkumab.

- No specific pattern of SAEs was identified.

Through Week 24, the overall SAE rates per 100 subject-years of follow-up were low and comparable across the treatment groups; 4.04, 5.23, and 9.26 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively. The SOC with the highest SAE rates was Infections and infestations with similar rates per 100 subject years of follow-up for the guselkumab q8w (0), guselkumab q4w (1.74), and placebo (2.89) groups.

Through the data cut, SAEs were reported at a frequency of 5.3% in the guselkumab 100 mg q8w group and 4.8% in the guselkumab 100 mg q4w group. There was no increased risk of an SAE in the guselkumab q4w group compared with the guselkumab q8w group.

- Infections and infestations was the SOC in which the highest proportions of subjects reported SAEs; 4 (1.1%) subjects in the guselkumab q8w group and 4 (1.1%) subjects in the guselkumab q4w group.

- All individual SAEs were reported in single subjects in either the guselkumab q8w or the guselkumab q4w group, except for foot deformity and pulmonary embolism both of which were reported in 2 subjects in the guselkumab q4w group.

- No specific pattern of SAEs was identified.

The event rates (per 100 subject-years of follow-up) for SAEs in the guselkumab q8w and q4w groups through the data cut were consistent with those in the same groups through Week 24. Through the data cut, the overall SAE rates per 100 subject-years of follow-up were similar for the guselkumab q8w (5.90) and q4w (5.12) groups, as well as for the combined guselkumab q4w group (6.55). The SOC with the highest SAE rates was Infections and infestations with similar rates per 100 subject-years of follow-up for the guselkumab q8w (1.34), guselkumab q4w (1.08), and the guselkumab q4w combined (1.59) groups.

SAEs listed in PSA3001

In the Guselkumab 100 mg q8w group, SAEs included cervical dysplasia, adhesion ileus, cellulitis left hand, multiple myeloma, supraventricular arrhythmia, hand fracture, right renal colic, acute bronchitis with bronchospasm. In the Guselkumab 100 mg q4w group, SAEs included foot deformity, worsening of breast enlargement and iliofemoral venous thrombosis. All outcomes were reported as recovered with the exception of the subjects with multiple myeloma and iliofemoral venous thrombosis, the drug was withdrawn from the subject with multiple myeloma. Cervical dysplasia and cellulitis were reported as possibly related to the study drug and all other SAEs were assessed by the investigator as unrelated/doubtful related to the study drug. In the Placebo to Guselkumab 100 mg q4w group, SAEs included head injury due to motor vehicle accident, atrial fibrillation and left-sided pyelonephritis which were all assessed by the investigator as unrelated to the study drug, the outcomes reported as recovered.

SAEs listed in PSA3002

In the Guselkumab 100 mg q8w group, SAEs included acute cystitis and pneumonia in the same subject, obesity, pyrexia of probable urinary origin, endometriosis, urolithiasis, exacerbation of psoriatic arthropathy, ankle fracture, unstable angina and diverticulitis in the same subject, coronary artery disease, pancreatitis, cholecystitis and post cholecystectomy syndrome in the same subject. Cystitis and pneumonia in the same subject were assessed by the investigator as possibly related to the study drug, Pyrexia of probable urinary origin was assessed as having a probable relation to the study drug otherwise the remaining SAEs were reported as unrelated or doubtful related. The outcomes of all possibly related SAEs were reported as recovered/resolved.

In the Guselkumab 100 mg q4w group, SAEs included Influenza B pneumonia, umbilical hernia, blue toe syndrome, pulmonary embolism, pneumonia, Rupture of the biceps brachii muscle, ischaemic stroke, osteoarthritis of left foot, acute oophoritis, foot deformity, multiple injuries, acute Hep B, femur fracture, tibia fracture and metal poisoning. Pneumonia and oophoritis were assessed by the investigator as possibly related to the study drug, the remaining SAEs otherwise were reported as unrelated or doubtful related. The outcomes of all possibly related SAEs were reported as recovered/resolved.

In the Placebo to Guselkumab 100 mg q4w group, SAEs included goitre, cholecystolithiasis and goitre in the same subject, influenza, tracheitis, Bilateral Extrapyramidal Syndrome, poly-trauma, metrorrhagia and endometrial hyperplasia in the same subject, right sided pneumonia, dysfunctional uterine bleeding, pericarditis as 2 reported events in the same subject, iliofemoral venous thrombosis and acute purulent periostitis of the lower jaw from 2-3rd tooth. Influenza, tracheitis, iliofemoral venous thrombosis and pericarditis were reported as possibly related to the study drug and all other SAEs were assessed by the investigator as unrelated/doubtful related to the study drug. To note pericarditis was reported as 2 events in the same subject, the 1st episode assessed as doubtful related and the 2nd episode as related. All outcomes were reported as recovered with the exception of the subjects with Bilateral Extrapyramidal Syndrome, endometrial hyperplasia. The outcomes of possibly related SAEs were all reported as recovered/resolved.

Laboratory findings

Hematology

Study PSA2001

- A numerical trend of greater reduction in mean change from baseline in WBC and neutrophil counts in the guselkumab group compared to placebo was observed over time through Week 24. At Week 24, the mean change from baseline for WBC count was -0.755 x 10^9/L for the guselkumab group and 0.188 x 10^9/L for the placebo group and the mean change from baseline for neutrophil count was -0.860 x 10^9/L for the guselkumab group and 0.038 x 10^9/L for the placebo group. After Week 24, the numerical trend was also observed in the placebo → guselkumab crossover group. A shift in neutrophil count from within normal reference range to below normal reference range was more frequently observed in the guselkumab group (15.7%) compared with the placebo group (4.3%) through Week 24. Neutrophil count decreases meeting NCI-CTCAE Grade 2 or 3 were infrequent through Week 24, occurring in 3 (3.0%) subjects and 1 (1.0%) subject, respectively, in the guselkumab group. Neutrophil count decreases meeting NCI-CTCAE Grade 2 or 3 were also infrequent through Week 56, occurring in 3 (2.3%) subjects and 1 (0.8%) subject, respectively, in the combined guselkumab group. The majority of cases of neutrophil count decrease were transient and reversible, resolved spontaneously without treatment and were not associated with infections, and did not result in discontinuation of study agent or study, except for 1 subject.

- A numerical trend of greater reduction in mean change from baseline in platelets in the guselkumab group compared to placebo was observed over time through Week 24. At Week 24, the mean change from baseline for platelet count was -17.7 x 10^9/L for the guselkumab group and 4.8 x 10^9/L for the placebo group. After Week 24, the numerical trend was also observed in the placebo → guselkumab crossover group. Through Week 24, a total of 2 (1.7%) subjects in the combined guselkumab group had a shift in platelets to below normal reference range. In both subjects, the decrease in platelets occurred before Week 16 and was transient and reversible. Through Week 56, 1 additional subject in the placebo → guselkumab crossover group, shifted from within normal reference range to below normal reference range. Of the 3 cases, none met NCI-CTCAE Grade 2 or more.

- Through Week 24 and through Week 56, no consistent, potentially clinically meaningful differences or trends were observed between guselkumab and placebo on other hematology parameters.

Pooled Phase 3 Psoriatic Arthritis Studies

Through Week 24, there were no clinically important trends observed in changes from baseline between the guselkumab and placebo groups for hemoglobin or lymphocytes.

Changes from baseline through Week 24 in neutrophil, WBC, and platelet counts are described below.

Neutrophils

Through Week 24, the proportion of subjects with a Grade 1 or higher post-baseline decrease in neutrophil count was slightly higher in the guselkumab q8w (7.2%) and q4w (7.8%) groups compared with the placebo group (4.3%) and most post-baseline decreases in neutrophil counts were Grade 1. Grade 2 or higher decreases in neutrophil counts were reported in few subjects treated with guselkumab (13 [1.7%] subjects) in the combined guselkumab group) and slightly more frequently in subjects in the guselkumab 100 mg q8w (1.6%) and 100 mg q4w (1.9%) groups compared with the placebo group (1.1%). Among guselkumab-treated subjects, there were no Grade 3 decreases in neutrophil counts. There was 1 Grade 4 decrease in neutrophil count in a subject in the guselkumab q4w group with concomitant etoricoxib treatment; a neutrophil count of 0.47 x 10^9/L was reported at the Week 8 visit. A retest performed 6 days later showed the neutrophil count had returned to within normal limits (2.59 ×10^9/L). The subject had other Grade 2 or higher neutrophil counts decreased (Grade 2: 1.03 ×1 0^9/L at Week 4 and Grade 3: 0.64×10^9/L at Week 12) that returned to normal limits when retests were performed prior to the next dosing visit and the study agent was not interrupted. The Grade 1 or higher decreases in neutrophil counts were comparable in the guselkumab q8w and q4w groups, generally resolved spontaneously without treatment, and were not associated with study agent interruption or discontinuation.

Through Week 24, among subjects with a Grade 2 or higher decrease in neutrophil count, no serious infections were reported and a single case of a nonserious viral URTI infection was reported in a guselkumab-treated subject.

A numerical trend of a greater mean reduction from baseline in neutrophil counts in the guselkumab groups compared with the placebo group was observed through Week 24. At Week 24, the mean change from baseline in neutrophil count was -0.7 x 10^9/L in the guselkumab q8w group and -0.6 x 10^9/L in the guselkumab q4w group compared with -0.2 x 10^9/L in the placebo group.

From baseline to Week 24, a shift in neutrophil count from within the normal range to below the normal range was reported in a greater proportion of subjects in the guselkumab groups (2.2% for q8w and 2.8% for q4w) compared with the placebo group (0.7%).

Through Week 24, guselkumab had no consistent effect on neutrophil count decreases across age and BMI subgroups. Among subjects using MTX at baseline, Grade 2 or higher decreases in neutrophil counts were reported more frequently in the guselkumab q8w (2.9%) and guselkumab q4w (1.9%) groups compared with the placebo group (0.9%). Among subjects using no non-biologic DMARDs at baseline, Grade 2 or higher decreases in neutrophil counts were 0, 2.5%, and 1.7% in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively. Guselkumab had no consistent effect on neutrophil count decreases across subgroups with or without baseline use of oral corticosteroids or latent TB treatment.

WBCs

Through Week 24, the proportion of subjects with a Grade 1 or higher post-baseline decreases in WBC counts was slightly higher in the guselkumab q8w (8.0%) and q4w (6.7%) groups compared with the placebo group (3.5%) and most post-baseline decreases in WBC counts were Grade 1. Grade 2 decreases in WBC counts were reported in few subjects treated with guselkumab (1.5% in the combined guselkumab group) and slightly more frequently in subjects in the guselkumab q8w (1.1%) and guselkumab q4w (1.9%) groups compared with the placebo group (0.8%). There were no Grade 3 or 4 decreases in WBC counts. The Grade 1 or higher decreases in WBC counts were comparable in the guselkumab q8w and q4w groups, generally resolved spontaneously without additional treatment, were not associated with study agent interruption or discontinuation. The decreases in WBC counts were primarily due to decreases in neutrophil counts.

A numerical trend of a greater mean reduction from baseline in WBC counts in the guselkumab groups compared with the placebo group was observed through Week 24. At Week 24, the mean change from baseline in WBC count was -0.7 x 10^9/L in the guselkumab q8w group, -0.6 x 10^9/L in the guselkumab q4w group, and -0.2 x 10^9/L in the placebo group.

Through Week 24, guselkumab had no consistent effect on WBC count decreases across age and BMI subgroups. As observed with neutrophil counts, among subjects using MTX at baseline, Grade 2 or higher decreases in WBC counts were reported more frequently in the guselkumab q8w (1.9%) and guselkumab q4w (2.3%) groups compared with the placebo group (0.9%). Among subjects using no non-biologic DMARDs at baseline, Grade 2 or higher decreases in WBC counts were 0, 1.7%, and 0.8% in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively. Guselkumab had no consistent effect on WBC count decreases across subgroups with or without baseline use of oral corticosteroids or latent TB treatment.

Platelets

Through Week 24, the proportions of subjects with Grade 1 or higher decreases in platelet counts were low and comparable across each of the guselkumab q8w (2.6%) and q4w (1.6%) groups and the placebo group (1.6%) as well as between the guselkumab q4w and guselkumab q8w groups. Most decreases in platelets were Grade 1. Grade 2 decreases in platelet counts were infrequent (2 subjects in the guselkumab q8w group) and there were no Grade 3 or 4 decreases in platelet counts. The Grade 1 or higher decreases in platelet counts were transient, resolved spontaneously without treatment, did not lead to study agent interruption or discontinuation, and were not associated with bleeding events.

A numerical trend of a greater mean reduction from baseline in platelets in the guselkumab groups compared with the placebo group was observed through Week 24. At Week 24, the mean change in platelet count from baseline was -21.7 x 10^9/L in the guselkumab q8w group, -21.0 x 10^9/L in the guselkumab q4w group, and -3.4 x 10^9/L in the placebo group.

Through Week 24, guselkumab had no consistent effect on platelet count decreases across age, BMI, and baseline medication use subgroups.

Table 1: Number of Subjects with Post-baseline Hematology Laboratory Values by Maximum NCI-CTCAE Toxicity Grade through Week 24; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Placebo-Controlled Period through Week 24[a]			
		Guselkumab		
	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	372	375	373	748
Neutrophil count decreased[c]				
N	370	373	371	744
Grade 1	12 (3.2%)	21 (5.6%)	22 (5.9%)	43 (5.8%)
Grade 2	3 (0.8%)	6 (1.6%)	6 (1.6%)	12 (1.6%)
Grade 3	1 (0.3%)	0	0	0
Grade 4	0	0	1 (0.3%)	1 (0.1%)
White blood cell count decreased[d]				
N	370	373	371	744
Grade 1	10 (2.7%)	26 (7.0%)	18 (4.9%)	44 (5.9%)
Grade 2	3 (0.8%)	4 (1.1%)	7 (1.9%)	11 (1.5%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Platelet count decreased[e]				
N	370	373	371	744
Grade 1	6 (1.6%)	8 (2.1%)	6 (1.6%)	14 (1.9%)
Grade 2	0	2 (0.5%)	0	2 (0.3%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0

LLL=lower limit of normal; NCI-CTCAE=National Cancer Institute – Common Terminology Criteria for Adverse Events.
Note: N is the number of subjects with at least one post-baseline assessment for the specific lab test within the time period.
[a]: For subjects in all treatment groups who discontinued study treatment early with the last study treatment (placebo or guselkumab) administrated prior to Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.
[b]: For subjects in placebo group who changed treatment from placebo to guselkumab due to crossover or inadvertently, only data prior to first administration of guselkumab were included in this group. Data on and after the first administration of guselkumab were not included in this group.
[c] Grade 1: <LLN-1.5 x 10^9/L; Grade 2: <1.5 -1.0 x 10^9/L; Grade 3: <1.0-0.5 x 10^9/L; Grade 4: <0.5 x 10^9/L
[d] Grade 1: <LLN-3.0 x 10^9/L; Grade 2: <3.0 -2.0 x 10^9/L; Grade 3: <2.0-1.0 x 10^9/L; Grade 4: <1.0 x 10^9/L
[e] Grade 1: <LLN-75.0 x 10^9/L; Grade 2: <75.0 -50.0 x 10^9/L; Grade 3: <50.0-25.0 x 10^9/L; Grade 4: <25.0 x 10^9/L
Adapted from: [TSFLABH01S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFLABH01S12.SAS] 20JUN2019, 10:19

Through the data cut, there were no clinically important trends observed in change from baseline for hemoglobin or lymphocytes.

Neutrophils

As through Week 24, through the data cut, the proportion of subjects reporting a decrease in neutrophil counts was low and most post-baseline decreases in neutrophil counts were Grade 1. The proportions of subjects who reported Grade 1 or greater decreases in neutrophil counts were comparable in the guselkumab q8w and guselkumab q4w groups. As through Week 24, decreases in neutrophil counts generally resolved spontaneously without additional treatment, and were not associated with study agent interruption or discontinuation. Compared with through Week 24, through the data cut, there was no disproportional increase in the proportions of subjects reporting a decrease in neutrophil counts.

Among guselkumab-treated subjects with a Grade 2 or higher decrease in neutrophil count there were no serious infections and few nonserious infections were reported.

Among all guselkumab-treated subjects, at most timepoints through the data cut, the mean change from baseline in neutrophil count was -0.4 to -0.7 x 10^9/L; the mean decrease was slightly greater at later timepoints (ie, Week 68 and later) that included fewer subjects. The mean change from baseline in neutrophil count was similar in the guselkumab q8w and q4w groups through the data cut.

Through the data cut, guselkumab had no consistent effect on neutrophil count decreases across age and BMI subgroups. Among subjects not using non-biologic DMARDs, Grade 2 or higher decreases in neutrophil counts were reported in 0.8% of subjects in the guselkumab q8w group and 4.1% of subjects in the guselkumab q4w group while in subjects using MTX, Grade 2 or higher decreases in neutrophil counts were reported in 4.4% of subjects in the guselkumab q8w group and 4.7% of subjects in the guselkumab q4w group. Guselkumab had no consistent effect on neutrophil count decreases across subjects with or without baseline use of oral corticosteroids or latent TB treatment.

WBCs

As through Week 24, through the data cut, the proportion of subjects reporting a decrease in WBC counts was low and most post-baseline decreases in WBC counts were Grade 1. The proportions of subjects who reported Grade 1 and 2 decreases in WBC counts were comparable in the guselkumab q8w and guselkumab q4w groups and no subjects reported Grade 3 or 4 decreases in WBC counts. As through Week 24, the decreases in WBC counts generally resolved spontaneously without additional treatment, were not associated with study agent interruption or discontinuation, and were primarily due to decreases in neutrophil counts.

Among all guselkumab-treated subjects, at most timepoints through the data cut the mean change from baseline in WBC count was -0.3 to 0.7 x 10^9/L; the mean decrease was slightly greater at later timepoints (ie, Week 68 and later) that included fewer subjects. The mean change from baseline in WBC count was similar in the guselkumab q8w and q4w groups through the data cut.

Through the data cut, guselkumab had no consistent effect on WBC count decreases across age and BMI subgroups. Among subjects not using non-biologic DMARDs, Grade 2 or higher decreases in WBC counts were reported in 0.8% of subjects in the guselkumab q8w group and 2.5% of subjects in the guselkumab q4w group while in subjects using MTX, Grade 2 or higher decreases in WBC counts were reported in 2.9% of subjects in the guselkumab q8w and 2.8% of subjects in the guselkumab q4w groups. Guselkumab had no consistent effect on WBC count decreases across subjects with or without baseline use of oral corticosteroids or latent TB treatment.

Platelets

The proportions of subjects with decreases in platelet counts through the data cut, as through Week 24, were low and comparable across all treatment groups. As through Week 24, through the data cut, the majority of the decreases in platelet counts were Grade 1 and there were few Grade 2 decreases in platelet counts. After Week 24 and through the data cut, a Grade 3 decrease in platelet counts was observed in 1 subject in the guselkumab 100 mg q8w group. This subject had Grade 1 thrombocytopenia at baseline and was then observed to have transient decreases in platelet counts at Weeks 20 and 28 which returned to baseline upon repeat testing prior to the next dosing visit without interruption of dosing. As through Week 24, the decreases in platelet counts recovered spontaneously without treatment and were not associated with study agent interruption or discontinuation. No bleeding events were reported in subjects with decreased platelet counts.

Among all guselkumab-treated subjects, at most timepoints through the data cut the mean decrease from baseline in platelet count was <25 x 10^9/L; the mean decrease was slightly greater at later timepoints (ie, Week 84 and later) that included fewer subjects. The mean change from baseline in platelet count was similar in the guselkumab q8w and q4w groups through the data cut.

Through the data cut, guselkumab had no consistent effect on platelet count decreases across age, BMI, and baseline medication use subgroups.

Table 1: Number of Subjects with Post-baseline Hematology Laboratory Values by Maximum NCI-CTCAE Toxicity Grade through Data Cut; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Guselkumab				
	100 mg q8w	100 mg q4w	Placebo → 100 mg q4w[a]	100 mg q4w Combined[a]	All Combined[a]
Analysis set: Safety Analysis Set	375	373	352	725	1100
Neutrophil count decreased[b]					
N	373	371	351	722	1095
Grade 1	36 (9.7%)	29 (7.8%)	13 (3.7%)	42 (5.8%)	78 (7.1%)
Grade 2	10 (2.7%)	13 (3.5%)	3 (0.9%)	16 (2.2%)	26 (2.4%)
Grade 3	2 (0.5%)	1 (0.3%)	2 (0.6%)	3 (0.4%)	5 (0.5%)
Grade 4	0	1 (0.3%)	0	1 (0.1%)	1 (0.1%)
White blood cell count decreased[c]					
N	373	371	351	722	1095
Grade 1	31 (8.3%)	29 (7.8%)	20 (5.7%)	49 (6.8%)	80 (7.3%)
Grade 2	7 (1.9%)	9 (2.4%)	2 (0.6%)	11 (1.5%)	18 (1.6%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Platelet count decreased[d]					
N	373	371	351	722	1095
Grade 1	11 (2.9%)	8 (2.2%)	7 (2.0%)	15 (2.1%)	26 (2.4%)
Grade 2	2 (0.5%)	0	0	0	2 (0.2%)
Grade 3	1 (0.3%)	0	0	0	1 (0.1%)
Grade 4	0	0	0	0	0

LLN=lower limit of normal; NCI-CTCAE=National Cancer Institute – Common Terminology Criteria for Adverse Events.
Note: N is the number of subjects with at least one post-baseline assessment for the specific lab test within the time period.
[a]: For subjects in placebo group who changed treatment from placebo to guselkumab due to crossover or inadvertently, only data on and after first administration of guselkumab were included in this group. Data prior to the first administration of guselkumab were not included in this group
[b] Grade 1: <LLN-1.5 x 10^9/L; Grade 2: <1.5 -1.0 x 10^9/L; Grade 3: <1.0-0.5 x 10^9/L; Grade 4: <0.5 x 10^9/L
[c] Grade 1: <LLN-3.0 x 10^9/L; Grade 2: <3.0 -2.0 x 10^9/L; Grade 3: <2.0-1.0 x 10^9/L; Grade 4: <1.0 x 10^9/L
[d] Grade 1: <LLN-75.0 x 10^9/L; Grade 2: <75.0 -50.0 x 10^9/L; Grade 3: <50.0-25.0 x 10^9/L; Grade 4: <25.0 x 10^9/L

Adapted from: [TSFLABH01S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFLABH01S12.SAS] 207JUN2019,

Across Psoriatic Arthritis and Psoriasis

In the pooled Phase 3 PsA studies, through Week 16, the proportion of subjects with a Grade 2 or higher post-baseline decrease in neutrophil count was comparable across treatment groups; 1.1%, 1.6%, and 1.1% for the guselkumab 100 mg q8w, guselkumab 100 mg q4w, and placebo groups, respectively; through Week 24, the proportion of subjects with a Grade 2 or higher post-baseline decrease in neutrophil count was slightly higher in the guselkumab groups than the placebo group. Through Week 16 in the pooled PSO3001 and PSO3002 studies, the proportion of subjects with a Grade 2 or higher post-baseline decrease in neutrophil count was comparable between the guselkumab 100 mg sq8w group (0.7%) and the placebo group (0.7%).

Through Week 16 in the pooled Phase 3 PsA studies, the proportion of subjects with a Grade 2 or higher post-baseline decrease in WBC count was higher in the guselkumab q4w group (1.9%) compared with the

guselkumab q8w (0.8%) and placebo (0.5%) groups. Through Week 16 in the pooled PSO3001 and PSO3002 studies, 0.4% of subjects in the guselkumab q8w group and no subjects in the placebo group had a Grade 2 or higher post-baseline decrease in WBC count.

Through Week 16 in the pooled Phase 3 PsA studies, no subjects had Grade 2 or greater decreases in platelet counts. Through Week 16 in the pooled PSO3001 and PSO3002 studies, Grade 2 decreases in platelet counts were reported in 1 (0.1%) subject in the guselkumab q8w group and 1 (0.2%) subject in the placebo group and there were no Grade 3 or 4 platelet count decreases.

A greater frequency of decreases in neutrophil counts and WBC counts was observed with longer duration of exposure through 1 year. The proportions of subjects who experienced neutrophil count decreases of CTCAE Grade ≥1 were 12.9% and 11.6% in the guselkumab q8w and every 4 weeks (q4w) groups, respectively, and 10.2% in all guselkumab-treated subjects through 1 year. The proportions of subjects who experienced WBC count decreases of CTCAE Grade ≥1 were 10.5% and 10.3% in the guselkumab q8w and q4w groups, respectively, and 9.2% in all guselkumab-treated subjects through 1 year. No Grade 3 or higher WBC count decrease was observed through 1 year. Grade ≥2 neutrophil count decreases and Grade 2 WBC count decreases in guselkumab-treated subjects were generally not associated with infections. Mean values for neutrophil counts and WBC counts in the guselkumab q8w and q4w groups did not further decrease from Week 24 through 1 year of treatment.

Compared to the proportion of subjects with a shift in platelet count from within/above reference range at baseline to below reference range post baseline in the placebo-controlled period, as expected, a greater proportion of subjects with shifts was observed with longer duration of exposure through 1 year. The proportions of subjects with a shift in platelet count from within/above reference range at baseline to below reference range post baseline in the placebo-controlled period or through 1 year were 1.9% and 3.0% in the q8w group, and 1.6% and 3.0% in the q4w group, respectively. There was no further decrease of mean platelet counts from Week 24 through 1 year. Mean platelet counts appeared to plateau 12 to 16 weeks after first treatment of guselkumab at Week 0.

Chemistry

Study PSA2001

- Through Week 24 and through Week 56, no consistent, potentially clinically meaningful differences or trends were observed to suggest an effect of guselkumab on any of the chemistry laboratory parameters evaluated, including fasting glucose and fasting lipids (total cholesterol, LDL, HDL, and triglycerides). Abnormal chemistry laboratory values with the NCI-CTCAE toxicity grade ≥2 were infrequent through Week 56 in the guselkumab-treated subjects.
- The mean change from baseline in ALT at Week 24 was 1.8 U/L in the guselkumab group and -0.4 U/L in the placebo group and at Week 56 the mean change from baseline was 3.2 U/L in the guselkumab group.
- The mean change from baseline in AST at Week 24 was 1.3 U/L in the guselkumab group and 1.0 U/L in the placebo group and at Week 56 the mean change from baseline was 2.3 U/L in the guselkumab group.
- Through Week 24, a Grade 2 or higher increase in ALT was reported 1 (2.0%) subject in the placebo group. Through Week 56, a Grade 2 or higher increase in ALT was reported in 4 (4.0%) subjects in the guselkumab group and 1 (2.0%) subject in the placebo group.
- Through Week 24, a Grade 2 or higher increase in AST was reported 3 (3.0%) subjects in the placebo group. Through Week 56, a Grade 2 or higher increase in AST was reported in 4 (4.0%) subjects in the guselkumab group, 1 (3.6%) subject who crossed over from placebo to guselkumab, and no subjects in the placebo group.

Pooled Phase 3 Psoriatic Arthritis Studies

Through Week 24, there were no clinically important trends observed in change from baseline for alkaline phosphatase, bilirubin, creatinine, glucose, potassium, sodium, albumin, and urate.

Increases in ALT and AST through Week 24 are discussed below.

Increased ALT and AST

Through Week 24, the proportions of subjects with Grade 1 or higher post-baseline increases in ALT were slightly higher in the guselkumab 100 mg q4w (38.8%) group compared with the guselkumab 100 mg q8w (30.1%) and placebo (32.3%) groups. The proportions of subjects with Grade 1 or higher post-baseline increases in AST were also slightly higher in the guselkumab q4w (24.8%) group compared with the guselkumab q8w (20.9%) and placebo (21.7%) groups. Most post-baseline increases in ALT and AST were Grade 1. The Grade 1 or higher increases in ALT and AST were generally transient, mostly less than 2 times the upper limit of normal, did not result in study agent interruption or discontinuation, and were not associated with clinically significant increases in bilirubin.

Grade 2 or higher increases in ALT and AST occurred infrequently through Week 24. Grade 2 or higher increases in ALT were reported slightly more frequently in the guselkumab q4w (3.8%) group compared with the guselkumab q8w (1.9%) and placebo (2.1%) groups. Grade 2 or higher increases in AST were reported slightly more frequently in the guselkumab q8w (2.1%) and guselkumab q4w (3.2%) groups compared with the placebo (1.6%) group and slightly more frequently in the guselkumab q4w group compared with the guselkumab q8w group. Grade 2 or higher increases in ALT or AST were generally transient, not associated with clinically significant increases in bilirubin, and did not result in study agent interruption or discontinuation, except in 3 subjects in the guselkumab 100 mg q4w group in PSA3002. In 1 of these subjects, who had a history of alcohol use and MTX use at baseline, study agent was interrupted due to the AEs of AST increased, ALT increased, cholecystitis chronic, chronic pancreatitis, and fatty liver; this subject was discontinued after the Week 24 visit. In the other 2 subjects, the study agent was discontinued due to an AE of drug-induced liver injury (drug [isoniazid]- induced hepatitis) in 1 subject and an SAE of acute hepatitis B in 1 subject.

Evaluations of individual cases with Grade 2 or higher elevations in ALT or AST indicated that there were no apparent patterns with regard to timing of onset and duration of elevations, most events were transient and resolved without interruption of study agent, and most subjects had confounding concomitant medications, alcohol use, and or medical conditions.

At Week 24, the mean change from baseline in ALT was 3.5 U/L in the guselkumab q8w group, 2.9 U/L in the guselkumab q4w group, and 0.8 U/L in the placebo group. At Week 24, the mean change from baseline in AST was 3.7 U/L in the guselkumab q8w group, 2.4 U/L in the guselkumab q4w group, and 1.4 U/L in the placebo group.

In general, through Week 24, guselkumab had no consistent effect on ALT and AST increases across age and BMI subgroups.

Through Week 24, across all treatment groups, Grade 2 or higher increases in ALT were generally reported more frequently in subjects using MTX at baseline than in subjects not using non-biologic DMARDs at baseline. In subjects with baseline use of MTX, Grade 2 or higher increases in ALT were reported slightly more frequently in subjects in the guselkumab q4w group (4.2%) compared with the guselkumab q8w (2.4%) and placebo (2.7%) groups.

Through Week 24, in subjects with baseline use of MTX, Grade 2 or higher increases in AST were reported slightly more frequently in subjects in the guselkumab q8w (1.9%) and guselkumab q4w (2.8%) groups compared with the placebo (0.9%) group.

Through Week 24, in the small number of subjects with baseline use of oral corticosteroids, Grade 2 or higher increases in ALT and AST increases were reported in a slightly higher proportion of subjects in the guselkumab combined (q8w and q4w) group compared with the placebo group.

Through Week 24, in subjects without baseline use of latent TB treatment, Grade 2 or higher increases in ALT and AST increases were reported in a slightly higher proportion of subjects in the guselkumab combined (q8w and q4w) group compared with the placebo group. This trend was not observed in the small number of subjects with baseline use of latent TB treatment.

Table 1: Number of Subjects with Post-baseline Clinical Chemistry Laboratory Values by Maximum NCI-CTCAE Toxicity Grade through Week 24; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Placebo-Controlled Period through Week 24[a]			
		Guselkumab		
	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	372	375	373	748
Alanine Aminotransferase Increased				
N	370	373	371	744
Grade 1[c]	111 (30.1%)	105 (28.2%)	130 (35.0%)	235 (31.6%)
Grade 2[d]	5 (1.4%)	4 (1.1%)	10 (2.7%)	14 (1.9%)
Grade 3[e]	2 (0.5%)	3 (0.8%)	4 (1.1%)	7 (0.9%)
Grade 4[f]	1 (0.3%)	0	0	0
Aspartate Aminotransferase Increased				
N	369	373	371	744
Grade 1[c]	74 (20.1%)	70 (18.8%)	80 (21.6%)	150 (20.2%)
Grade 2[d]	2 (0.5%)	6 (1.6%)	6 (1.6%)	12 (1.6%)
Grade 3[e]	4 (1.1%)	2 (0.5%)	6 (1.6%)	8 (1.1%)
Grade 4[f]	0	0	0	0

NCI-CTCAE=National Cancer Institute – Common Terminology Criteria for Adverse Events; ULN=upper limit of the normal range.
Note: N is the number of subjects with at least one post-baseline assessment for the specific lab test within the time period.
[a] For subjects in all treatment groups who discontinued study treatment early with the last study treatment (placebo or guselkumab) administrated prior to Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.
[b] For subjects in placebo group who changed treatment from placebo to guselkumab due to crossover or inadvertently, only data prior to first administration of guselkumab were included in this group. Data on and after the first administration of guselkumab were not included in this group.
[c] Grade 1 increase: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
[d] Grade 2 increase: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
[e] Grade 3 increase: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
[f] Grade 4 increase: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Adapted from: [TSFLABC01S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFLABC01S12.SAS] 20 JUN2019, 10:25

Through the data cut, there were no clinically important trends observed in change from baseline for alkaline phosphatase, bilirubin, creatinine, glucose, potassium, sodium, urate, and albumin.

Increased ALT and AST

Through the data cut, most increases in ALT and AST were Grade 1. The frequencies of Grade 1 and higher increases in ALT and AST were slightly higher in the guselkumab 100 mg q4w group compared with the guselkumab 100 mg q8w group. The frequencies of Grade 2 and higher increases in ALT and AST were also slightly higher in the guselkumab q4w group compared with the q8w group. Increases in ALT or AST were generally transient and did not result in study agent interruption or discontinuation, apart from what was described through Week 24.

Among all guselkumab-treated subjects, the mean change from baseline in ALT was generally an increase of approximately 1 to 3 U/L at all timepoints through the data cut; the mean increase was slightly greater at later timepoints (ie, Week 68 and later) that included fewer subjects at all timepoints through the data cut. Among all guselkumab-treated subjects, the mean change from baseline in AST was generally an increase of approximately 1.5 to 3.5 U/L at all timepoints through the data cut; the mean increase was slightly greater at later timepoints (ie, Week 76 and later) that included fewer subjects.

Through the data cut, guselkumab had no consistent effect on ALT and AST increases across age and BMI subgroups.

As through Week 24, increases in ALT and AST were generally reported more frequently in subjects treated with MTX at baseline than in subjects who did not use non-biologic DMARDs at baseline. In subjects with baseline use of MTX, Grade 2 or greater increases in ALT and AST were reported more frequently in the guselkumab q4w group (5.1% and 4.6%, respectively) compared with the q8w group (3.8% and 3.4%, respectively). In subjects who did not use non-biologic DMARDs at baseline, Grade 2 or greater increases in ALT were reported more frequently in the guselkumab q4w group (4.1%) compared with the q8w group (2.5%) and Grade 2 or greater increases in AST were similar between the guselkumab q8w (4.9%) and q4w (4.1%) groups.

Through the data cut, ALT and AST increases of Grade 2 or higher were reported in a slightly higher proportion of subjects in the guselkumab q4w group compared with q8w group in both subjects with and without baseline use of oral corticosteroids as well as subjects with and without baseline use of latent TB treatment.

Table 1: Number of Subjects with Post-baseline Clinical Chemistry Laboratory Values by Maximum NCI-CTCAE Toxicity Grade through Data Cut; Safety Analysis Set (Studies CNTO1959PSA3001 and CNTO1959PSA3002)

	Guselkumab				
	100 mg q8w	100 mg q4w	Placebo → 100 mg q4w[a]	100 mg q4w Combined[a]	All Combined[a]
Analysis set: Safety Analysis Set	375	373	352	725	1100
Alanine Aminotransferase Increased					
N	373	371	351	722	1095
Grade 1[b]	125 (33.5%)	150 (40.4%)	85 (24.2%)	235 (32.5%)	360 (32.9%)
Grade 2[c]	7 (1.9%)	15 (4.0%)	7 (2.0%)	22 (3.0%)	29 (2.6%)
Grade 3[d]	4 (1.1%)	4 (1.1%)	0	4 (0.6%)	8 (0.7%)
Grade 4[e]	0	0	0	0	0
Aspartate Aminotransferase Increased					
N	373	371	350	722	1095
Grade 1[b]	82 (22.0%)	101 (27.2%)	65 (18.6%)	166 (23.0%)	248 (22.6%)
Grade 2[c]	11 (2.9%)	13 (3.5%)	6 (1.7%)	19 (2.6%)	30 (2.7%)
Grade 3[d]	2 (0.5%)	6 (1.6%)	1 (0.3%)	7 (1.0%)	9 (0.8%)
Grade 4[e]	0	0	0	0	0

NCI-CTCAE=National Cancer Institute – Common Terminology Criteria for Adverse Events; ULN=upper limit of the normal range.

Note: N is the number of subjects with at least one post-baseline assessment for the specific lab test within the time period.

[a] For subjects in placebo group who changed treatment from placebo to guselkumab due to cross-over or inadvertently, only data on and after first administration of guselkumab were included in this group. Data prior to the first administration of guselkumab were not included in this group.

[b] Grade 1 increase: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal

[c] Grade 2 increase: >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal

[d] Grade 3 increase: >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal

[e] Grade 4 increase: >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Adapted from: [TSFLABC01S12.RTF] [CNTO1959\Z_SCS\DBR_2019_05\RE_PSA_SBLA\PROD\TSFLABC01S12.SAS] 20JUN2019, 10:25

Across Psoriatic Arthritis and Psoriasis

Through Week 16 in the pooled Phase 3 PsA studies, as well as through Week 16 in the pooled PSO3001 and PSO3002 studies, abnormal post-baseline chemistry laboratory values with CTCAE toxicity Grade ≥2 were infrequent and except for ALT and AST in the pooled Phase 3 PsA studies the rates were generally comparable across the treatment groups.

In the pooled Phase 3 PsA studies, through Week 16, the proportions of subjects with a Grade 2 or higher post-baseline increases in ALT was slightly higher in the guselkumab q4w group (2.4%) compared with the guselkumab q8w (1.1%), and placebo (1.6%) groups, this is consistent with data through Week 24. In the pooled PSO3001 and PSO3002 studies, through Week 16, Grade 2 or higher post-baseline increases in ALT were similar in the guselkumab q8w (1.6%) and placebo (1.2%) groups.

In the pooled Phase 3 PsA studies, through Week 16, the proportions of subjects with a Grade 2 or higher post-baseline increases in AST was slightly higher in the guselkumab q4w group (2.4%) compared with the guselkumab q8w (1.3%), and placebo (1.4%) groups; this is consistent with data through Week 24. Through Week 16 in the pooled PSO3001 and PSO3002 studies, Grade 2 or higher post-baseline increases in AST were similar in the guselkumab q8w (1.3%) and placebo (1.4%) groups.

Through 1 year, most post-baseline increases in ALT and AST were Grade 1 and the proportions of subjects with Grade 1 or higher post-baseline increases in ALT were higher in the guselkumab q4w (46.9%) group compared with the q8w group (36.2%). The proportions of subjects with Grade 1 or higher post-baseline increases in AST were also slightly higher in the guselkumab q4w (33.2%) group compared with the q8w group (26.3%). A greater frequency was observed with the longer duration of exposure through 1 year.

AEs reported in the Hepatobiliary disorders SOC were comparable between the guselkumab q4w (3.5%) and q8w (2.7%) groups. The majority of AEs reported through 1 year were preferred terms (PTs) related to hepatic steatosis for both the q4w (2.7%) and q8w (1.3%) groups. Through 1 year, 3 subjects in the guselkumab q4w group reported PTs of Drug-induced liver injury (DILI), Hepatitis toxic, and Hepatocellular injury (one subject each) and causality was assessed as related to the concomitant anti-TB therapy in all 3 subjects.

There were no events that satisfied the criteria for Hy's Law in guselkumab-treated subjects through 1 year.

In subjects with baseline MTX use, Grade 1 or higher increases in ALT were more frequent than in subjects without baseline MTX use.

In the guselkumab Phase 2/3 study in Crohn's disease, CNTO1959CRD3001 (EudraCT number: 2017 002195-13), a single case of toxic hepatitis with severe elevation of liver function tests meeting Hy's law criteria occurred in a subject who was randomized to receive guselkumab 1200 mg IV at Weeks 0, 4, and 8 followed by 200 mg SC q4w. A thorough review of the case and a comprehensive signal evaluation, including review of the biological plausibility of IL-23 blockade and DILI, and preclinical, clinical, and postmarketing data, was performed. Neither the detailed evaluation of the biological plausibility of IL-23 blockade and DILI that focused on possible genetic associations between the IL-23 pathway and liver injury, IL-23 pathway links to viral infections that might be associated with liver injury, and the role of IL-23 and IL-22 in liver biology, nor the toxicology findings for the compound, nor the clinical study data evaluation, demonstrated a biological basis for a causal relationship between this event and exposure to guselkumab.

A review of all postmarketing events reported with laboratory test results and/or with PTs relevant for liver injury did not identify any event of potential DILI attributed to guselkumab.

Safety in special populations

Intrinsic Factors

Age

Overall, in the pooled Phase 3 PsA studies safety analysis set, 42.9% of subjects were <45 years of age, 51.6% of subjects were ≥45 and <65 years of age, and 5.5% of subjects were ≥65 years of age.

In the <45 years of age subgroup only, AEs were reported more frequently in each of the guselkumab groups (48.3% for q8w and 48.4% for q4w) compared with the placebo group (40.3%). The proportions of subjects with SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in all age subgroups (ie, <45 years of age, ≥45 and <65 years of age, and ≥65 years of age).

No consistent differences were observed in the overall safety profile of guselkumab among age subgroups through Week 24 and the data cut.

Sex

Overall, in the pooled Phase 3 PsA studies safety analysis set, 52.1% of subjects were males.

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in both of the gender subgroups.

No consistent differences were observed in the overall safety profile of guselkumab between gender subgroups through Week 24 and the data cut.

Race

Overall, in the pooled Phase 3 PsA studies safety analysis set, approximately 96% of the subjects were white most of the other subjects were Asian; thus interpretation of data regarding the impact of race upon safety is limited due to the small number of subjects who were a race other than white.

Weight

Overall, 62% of subjects in the pooled Phase 3 PsA studies safety analysis set weighed ≤90 kg and 38% weighed >90 kg.

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in both of the weight subgroups (ie, ≤90 kg or >90 kg).

Overall, 40% of subjects in the pooled Phase 3 PsA studies safety analysis set were obese with a BMI ≥30 kg/m^2, 34.5% were overweight with BMI ≥25 to <30 kg/m^2, and 25.5% had a normal BMI (<25 kg/m^2).

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in all BMI subgroups (ie, (<25 kg/m^2, ≥25 to <30 kg/m^2, or ≥30 kg/m^2).

No consistent differences were observed in the overall safety profile of guselkumab among weight or BMI subgroups through Week 24 and the data cut.

C-Reactive Protein

At baseline, 52.9% of subjects in the pooled Phase 3 PsA studies safety analysis set had a CRP <1 mg/dL, 19.1% had a CRP of ≥1 to <2 mg/dL, and 28.0% had a CRP of ≥2 mg/dL.

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in all CRP subgroups (ie, <1 mg/dL, ≥1 to <2 mg/dL, and ≥2 mg/dL).

No consistent differences were observed in the overall safety profile of guselkumab among CRP subgroups through Week 24 and the data cut.

Body Surface Area Affected by Psoriasis

In the pooled Phase 3 PsA studies safety analysis set, the BSA affected by psoriasis at baseline was <3% in 21.1% of subjects, ≥3% to <10% in 32.4% of subjects, ≥10% to <20% in 19.9% of subjects, and ≥20% in 26.6% of subjects.

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, and serious infections were generally similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in all subgroups of BSA affected by psoriasis (ie, <3%, ≥3% to <10%, ≥10% to <20%, and ≥20%).

No consistent differences were observed in the overall safety profile of guselkumab among BSA affected by psoriasis subgroups through Week 24 and the data cut.

Extrinsic Factors

Geographic Region

At baseline, 30% of subjects were from sites in Russia, 26% were from sites in Ukraine, 17% were from sites in Poland, 8% were from sites in Western countries (USA, Canada, Spain, and Germany), and 19% were from sites in other countries (combining countries of Asia Pacific and Eastern European countries other than Russia, Ukraine, and Poland).

No consistent differences were observed in the overall safety profile of guselkumab among geographic regions through Week 24 and the data cut.

Oral Corticosteroid Use at Baseline

At baseline, 17.8% of subjects in the pooled Phase 3 PsA studies safety analysis set used oral corticosteroids.

In the small number of subjects with baseline use of oral corticosteroids, SAEs were reported more frequently in the guselkumab q4w (4.8%) group compared with the q8w (1.5%) and placebo (1.4%) groups through Week 24 and more frequently in the guselkumab q4w group (11.3%) compared with the guselkumab q8w group (5.9%) through the data cut. Also, among subjects with baseline use of oral corticosteroids, infections were reported more frequently in the guselkumab q4w group (24.2%) compared with the guselkumab q8w (11.8%) and placebo (15.9%) groups through Week 24; through the data cut, infections were reported at comparable frequencies in the guselkumab q8w (32.4%) and guselkumab q4w (33.9%) groups.

The proportions of subjects with AEs and serious infections were similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in both subjects with and without baseline use of oral corticosteroids.

Although the number of subjects who used oral corticosteroids at baseline was small, no consistent differences were observed in the overall safety profile of guselkumab by baseline use of corticosteroids through Week 24 and the data cut.

Baseline Use of Non-biologic DMARDs, Including MTX

Baseline use of non-biologic DMARDs (ie, MTX, SSZ, HCQ, and LEF) was reported in 67.8% of subjects (86.1% [n=654] used MTX and 13.8% [n=105] used non-MTX DMARDs) in the pooled Phase 3 PsA studies safety analysis set.

There was a general trend across the treatment groups for a slightly higher frequency of AEs and infections in subjects who reported baseline use of non-biologic DMARDs or MTX compared with subjects without baseline use of non-biologic DMARDs through Week 24 and the data cut.

Among the small number of subjects without baseline use of non-biologic DMARDs, through Week 24 infections were reported more frequently in the guselkumab q4w (23.1%) group compared with the guselkumab q8w (16.4%) and placebo (15.3%) groups; the difference between the guselkumab q8w and q4w groups was not seen through the data cut. In subjects with baseline use of MTX, through Week 24 and the data cut, the frequency of infection was not higher in the guselkumab q4w group (20.6% and 30.7%, respectively) compared with the guselkumab q8w group (23.0% and 38.3%, respectively).

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, and serious infections were similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) both in subjects with and without baseline use of non-biologic DMARDs, including subjects with baseline use of MTX.

No consistent differences were observed in the overall safety profile of guselkumab by baseline use of non-biologic DMARDs, including MTX, through Week 24 and the data cut.

Prior Use of Non-biologic Treatments

Prior use of non-biological treatments including DMARDs, systemic immunosuppressives, and oral apremilast was reported in 91% of subjects (1 treatment 59.8%, 2 treatments 23.9%, and ≥3 treatments 7.3%) in the pooled Phase 3 PsA studies safety analysis set.

There was a general trend across the treatment groups for a higher frequency of AEs and infections with an increase in the number of prior non-biological treatments to which subjects were exposed through Week 24 and the data cut.

In the small number of subjects without prior use of non-biologic treatments, through Week 24 AEs were reported more frequently in the guselkumab q4w group (58.3%) compared with the guselkumab q8w (33.3%) and placebo (50.0%) groups, and through the data cut AEs were reported more frequently in the guselkumab q4w group (69.4%) compared with the guselkumab q8w (52.8%) group. This trend was not observed in subjects with prior use of non-biological treatments.

In the small number of subjects without prior use of non-biologic treatments, through Week 24, infections were reported more frequently in the guselkumab q4w group (33.3%) compared with the guselkumab q8w (13.9%) and placebo (7.1%) groups, and through the data cut, infections were reported more frequently in the guselkumab q4w group (36.1%) compared with the guselkumab q8w group (22.2%). This trend was not observed in subjects with prior use of non-biological treatments.

The proportions of subjects with SAEs, AEs leading to discontinuation of study agent, and serious infections were similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) in all subgroups of prior use of non-biologic treatments.

No consistent differences were observed in the overall safety profile of guselkumab by prior use of non-biologic treatments through Week 24 and the data cut.

Prior Exposure to **anti-TNFα** Agents

Prior exposure to anti-TNFα agents was reported in 118 (31%) of the 381 subjects in PSA3001 (all subjects were biologic naïve in PSA3002).

Among subjects who reported prior exposure to anti-TNFα agents, infections were reported more frequently in the guselkumab q4w group (34.2%) compared with the guselkumab q8w (24.4%) and placebo (23.1%) groups through Week 24 and more frequently in the guselkumab q4w (50.0%) compared with the guselkumab q8w group (31.7%) through the data cut; this was not observed in subjects who did not have prior exposure to anti-TNFα agents.

The proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, and serious infections were similar between the guselkumab groups and the placebo group (through Week 24) and between the guselkumab q8w and q4w groups (through the data cut) both in subjects with and without prior exposure to anti-TNFα agents.

No consistent differences were observed in the overall safety profile of guselkumab by prior exposure to anti-TNFα agents through Week 24 and the data cut.

Through 1 year, SAEs were more frequent in the guselkumab q4w group compared with the q8w group. The rates of infections and serious infections in subjects using corticosteroids at baseline were similar between the guselkumab q4w and q8w groups through 1 year. The differences observed at Week 24 in the frequency of AEs and infections between the guselkumab q4w and q8w groups in subjects using non-biologic DMARDs at baseline were no longer present at 1 year, and the frequency of serious infections in subjects using non-biologic DMARDs at baseline was also comparable between the guselkumab q4w and q8w groups at 1 year. Through 1 year, among subjects who reported prior exposure to anti-TNFα agents, infections (but not serious infections) and AEs were reported more frequently in the guselkumab q4w group compared with the q8w group.

Safety related to drug-drug interactions and other interactions

As presented for the initial marketing application for psoriasis, an in vitro study using human hepatocytes showed that IL-23 at levels of 10 ng/mL did not alter human cytochrome P450 (CYP) enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). In a Phase 1 study in subjects with moderate-to-severe plaque psoriasis, changes in systemic exposures (maximum plasma concentration and area under the concentration-time curve from time 0 to infinity) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant, indicating that drug interactions between guselkumab and substrates of various CYP enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely.

Discontinuation due to adverse events

<u>Study PSA2001</u>

- Through Week 44, 2 (2.0%) subjects in the guselkumab group (1.6% in the guselkumab combined group) had AEs that subsequently resulted in discontinuation of study agent administration. One subject was discontinued due to leukopenia and neutropenia, and 1 subject was discontinued due to repeated episodes of pneumonia.

<u>Pooled Phase 3 Psoriatic Arthritis Studies</u>

The number of subjects who discontinued study agent due to an AE through Week 24 was low across all treatment groups; 5 (1.3%) subjects in the guselkumab 100 mg q8w group, 8 (2.1%) subjects in the guselkumab 100 mg q4w group, and 7 (1.9%) subjects in the placebo group.

- No individual AE led to discontinuation of guselkumab in more than 1 subject.

- Four subjects treated with guselkumab reported infections that led to discontinuation of study agent; bronchitis was reported in 1 subject in the guselkumab q8w group and acute hepatitis B, pneumonia influenzal, and rhinovirus infection were each reported in 1 subject in the guselkumab q4w group.

Through Week 24, the overall rates of AEs leading to discontinuation of study agent per 100 subject-years of follow-up were 2.88, 6.97, and 4.05 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively.

The number of subjects who discontinued study agent due to an AE through the data cut was low in both the guselkumab 100 mg q8w group (8 [2.1%]) and the guselkumab 100 mg q4w group (10 [2.7%] subjects.

- Injection site erythema resulted in discontinuation of guselkumab in 2 subjects in the guselkumab q4w group; no other AEs resulted in discontinuation of guselkumab in more than 1 subject in either the guselkumab q8w or q4w groups.
- Six subjects in the guselkumab q8w and q4w groups reported infections that led to discontinuation of study agent; in addition to acute hepatitis B, bronchitis, pneumonia influenzal, and rhinovirus infection reported through Week 24, paronychia (guselkumab q8w), and pneumonia necrotizing (guselkumab q8w), were reported through the data cut.

The event rates (per 100 subject-years of follow-up) for AEs leading to discontinuation of study agent in the guselkumab q8w and q4w groups through the data cut were consistent with those in the same groups through Week 24. Through the data cut, the overall rates of AEs leading to discontinuation of study agent per 100 subject-years of follow-up were 2.15, 4.04, and 3.72 for the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups, respectively.

Comparisons of Safety in Psoriatic Arthritis and Psoriasis

The overall proportions of subjects reporting AEs and AEs of infection through Week 16 were comparable across the guselkumab and placebo groups in both the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies. Through Week 16, the proportions of subjects reporting SAEs, AEs resulting in discontinuation of study agent, serious infections, AEs with severe intensity, and malignancies were low and comparable across the guselkumab and placebo groups in the pooled Phase 3 PsA studies as well as in the pooled PSO3001 and PSO3002 studies. Injection-site reactions were reported at a slightly higher frequency with guselkumab injections compared with placebo injections in both the pooled Phase 3 PsA studies and in the pooled PSO3001 and PSO3002 studies through Week 16.

Table 9: Overall Summary of Treatment-emergent Adverse Events over Placebo-controlled Period; Safety Analysis Set (Studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSA3001 and CNTO1959PSA3002)

	CNTO1959PSO3001 and CNTO1959PSO3002[a]		CNTO1959PSA3001 and CNTO1959PSA3002							
	Through Week 16		Through Week 16				Through Week 24			
		Guselkumab		Guselkumab				Guselkumab		
	Placebo[b]	100 mg q8w	Placebo[b]	100 mg q8w	100 mg q4w	Combined	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	422	823	372	375	373	748	372	375	373	748
Avg duration of follow up (weeks)	15.9	16.2	16.1	16.1	16.1	16.1	24.2	24.1	24.1	24.1
Avg number of study agent admins	10.6	10.8	4.0	4.0	4.0	4.0	5.9	5.9	5.9	5.9
Avg number of placebo admins	10.6	7.8	4.0	1.0	0.0	0.5	5.9	2.0	0.0	1.0
Avg number of guselkumab admins	-	3.0	-	3.0	4.0	3.5	-	3.9	5.9	4.9
Subjects with 1 or more AEs	197 (46.7%)	405 (49.2%)	145 (39.0%)	143 (38.1%)	152 (40.8%)	295 (39.4%)	176 (47.3%)	182 (48.5%)	182 (48.8%)	364 (48.7%)
Subjects with 1 or more serious AEs	6 (1.4%)	16 (1.9%)	7 (1.9%)	5 (1.3%)	5 (1.3%)	10 (1.3%)	12 (3.2%)	7 (1.9%)	8 (2.1%)	15 (2.0%)
Subjects with 1 or more AEs leading to discontinuation of study agent	4 (0.9%)	11 (1.3%)	4 (1.1%)	4 (1.1%)	5 (1.3%)	9 (1.2%)	7 (1.9%)	5 (1.3%)	8 (2.1%)	13 (1.7%)
Subjects with 1 or more AEs with severe intensity	8 (1.9%)	9 (1.1%)	2 (0.5%)	3 (0.8%)	2 (0.5%)	5 (0.7%)	6 (1.6%)	3 (0.8%)	2 (0.5%)	5 (0.7%)
Subjects with 1 or more infections	90 (21.3%)	191 (23.2%)	50 (13.4%)	53 (14.1%)	61 (16.4%)	114 (15.2%)	77 (20.7%)	73 (19.5%)	80 (21.4%)	153 (20.5%)
Subjects with 1 or more serious infections	1 (0.2%)	1 (0.1%)	1 (0.3%)	0	1 (0.3%)	1 (0.1%)	3 (0.8%)	1 (0.3%)	3 (0.8%)	4 (0.5%)
Subjects with 1 or more injection site reactions	13 (3.1%)	37 (4.5%)	0	5 (1.3%)	4 (1.1%)	9 (1.2%)	1 (0.3%)	5 (1.3%)	4 (1.1%)	9 (1.2%)
Subjects with 1 or more events of malignancy	0	1 (0.1%)	1 (0.3%)	2 (0.5%)	0	2 (0.3%)	1 (0.3%)	2 (0.5%)	0	2 (0.3%)
Subjects with 1 or more opportunistic infections	0	0	0	0	0	0	0	0	0	0
Subjects with 1 or more anaphylactic reactions or serum sickness reactions	0	0	0	0	0	0	0	0	0	0
Subjects with 1 or more events leading to death	0	0	0	0	0	0	2 (0.5%)	0	0	0

Note: Adverse events are coded using MedDRA Version 21.1. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
[a]: Subjects treated with adalimumab in CNTO1959PSO3001 and CNTO1959PSO3002 were excluded from the analyses.
[b]: For subjects in placebo group who changed treatment from placebo to guselkumab inadvertently prior to Week 16 in CNTO1959PSO3001 and CNTO1959PSO3002 or Week 24 in CNTO1959PSA3001 and CNTO1959PSA3002, only data prior to first administration of Guselkumab were included in the analyses. Data on and after the first administration of Guselkumab were not included.

Through Week 16, AEs reported in ≥5% of subjects in a guselkumab-treated group included ALT increased and nasopharyngitis in the pooled Phase 3 PsA studies and nasopharyngitis and URTI in the pooled PSO3001 and PSO3002 studies.

Adverse events reported more frequently with guselkumab compared with placebo (ie, in ≥1% of subjects in any guselkumab group and ≥2 times more frequently in the guselkumab combined group compared with the placebo group) in the pooled Phase 3 PsA studies through Week 16 included nasopharyngitis, ALT increased, AST increased, bronchitis, respiratory tract infection, injection site erythema, leukopenia, and neutrophil count decreased which is generally consistent with PsA data through Week 24. Nasopharyngitis and injection site erythema were previously identified as ADRs. Respiratory tract infection, bronchitis, transaminases increased, and neutrophil count decreased were identified as new ADRs from the pooled Phase 3 PsA studies. Adverse events of leukopenia were most commonly associated with decreased neutrophil count and were considered together with neutrophil count decreased. Through Week 16 in the pooled PSO3001 and PSO3002 studies, injection site erythema was reported more frequently with guselkumab compared with placebo (ie, in ≥1% of subjects in the guselkumab group and ≥2 times more frequently in the guselkumab group compared with the placebo group).

Through Week 16, the overall AE rates (per 100 subject-years of follow-up) in the guselkumab groups were comparable with those in the placebo groups in both the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies. Through Week 16, the overall AE rates per 100 subject-years of follow-up were 252.59, 238.27, and 228.68 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively, in the pooled Phase 3 PsA studies, and 330.11 and 316.87 for the guselkumab q8w and placebo groups, respectively, in the pooled PSO3001 and PSO3002 studies.

Through Week 16, the majority of AEs were of mild intensity in the pooled Phase 3 PsA studies (63.6%, 67.8%, and 60.7% of AEs reported in the guselkumab q8w, guselkumab q4w, and placebo groups, respectively) and in the pooled PSO3001 and PSO3002 studies (61.5% and 58.9% of AEs reported in the guselkumab q8w and placebo groups, respectively). The numbers of subjects reporting 1 or more AEs of

severe intensity were low and similar across treatment groups in the pooled Phase 3 PsA studies (3 [0.8%] subjects in the guselkumab q8w group, 2 [0.5%] subjects in guselkumab q4w group, and 2 [0.5%] subjects in the placebo group) as well as in the pooled PSO3001 and PSO3002 studies (9 [1.1%] subjects in the guselkumab q8w group and 8 [1.9%] subjects in the placebo group).

Serious Adverse Events

Through Week 16, the proportions of subjects reporting SAEs were low and similar between the guselkumab and placebo groups in the pooled Phase 3 PsA studies, as well as in the pooled PSO3001 and PSO3002 studies. In the pooled Phase 3 PsA studies through Week 16, SAEs were reported in 5 (1.3%) subjects in the guselkumab 100 mg q8w group, 5 (1.3%) subjects in the guselkumab 100 mg q4w group, and 7 (1.9%) subjects in the placebo group. In the pooled PSO3001 and PSO3002 studies through Week 16, SAEs were reported in 16 (1.9%) subjects in the guselkumab 100 mg q8w group and 6 (1.4%) subjects in the placebo group. Through Week 16 in the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, all individual SAEs were reported in single subjects; except non-cardiac chest pain which was reported in 2 subjects in the guselkumab group in the pooled PSO3001 and PSO3002 studies.

Through Week 16 in the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, the overall SAE rates (per 100 subject-years of follow-up) were low and comparable in the guselkumab and placebo groups. Through Week 16, the overall SAE rates per 100 subject-years of follow-up were 4.31, 4.35, and 6.09 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively, in the pooled Phase 3 PsA studies and 6.27 and 4.67 for the guselkumab q8w and placebo groups, respectively, in the pooled PSO3001 and PSO3002 studies.

Adverse Events Resulting in Discontinuation of Study Agent Administration

The proportions of subjects reporting AEs resulting in discontinuation of study agent through Week 16 were low and similar between the guselkumab and placebo groups in the pooled Phase 3 PsA studies as well as in the pooled PSO3001 and PSO3002 studies. In the pooled Phase 3 PsA studies through Week 16, AEs resulting in discontinuation of study agent were reported in 4 (1.1%) subjects in the guselkumab 100 mg q8w group, 5 (1.3%) subjects in the guselkumab 100 mg q4w group, and 4 (1.1%) subjects in the placebo group. In the pooled PSO3001 and PSO3002 studies through Week 16, AEs resulting in discontinuation of study agent were reported in 11 (1.3%) subjects in the guselkumab 100 mg q8w group and 4 (0.9%) subjects in the placebo group. Through Week 16 in both the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, no individual AE led to discontinuation of guselkumab in more than 1 subject.

Infection

Through Week 16 in the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, the overall proportions of subjects reporting AEs of infection were similar in the guselkumab and placebo groups. The proportions of subjects reporting at least 1 AE categorized as an infection by the investigator in the pooled Phase 3 PsA studies through Week 16 were 14.1% for the guselkumab 100 mg q8w group, 16.4% for the guselkumab 100 mg q4w group, and 13.4% for the placebo group. The proportions of subjects reporting at least 1 AE categorized as an infection by the investigator in the pooled PSO3001 and PSO3002 studies through Week 16 were 23.2% for the guselkumab 100 mg q8w group and 21.3% for the placebo group. Through Week 16 in both the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, the most frequently reported AEs of infection were nasopharyngitis and URTI.

Through Week 16, the overall AEs of infection rates per 100 subject-years of follow-up were 58.62, 60.00, and 48.69 for the guselkumab q8w, guselkumab q4w, and placebo groups, respectively, in the

pooled Phase 3 PsA studies, and 97.90 and 86.42 for the guselkumab q8w and placebo groups, respectively in the pooled PSO3001 and PSO3002 studies.

Through Week 16, the proportions of subjects reporting serious infections during the placebo controlled periods were low and similar between the guselkumab and placebo groups in the pooled Phase 3 PsA studies as well as in the pooled PSO3001 and PSO3002 studies. In the pooled Phase 3 PsA studies through Week 16, serious infections were reported in no subjects in the guselkumab q8w group, 1 (0.3%) subject in the guselkumab q4w group, and 1 (0.3%) subject in the placebo group. In the pooled PSO3001 and PSO3002 studies through Week 16, serious infections were reported in 1 (0.1%) subject in the guselkumab q8w group and 1 (0.2%) subject in the placebo group. Through Week 16 in both the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, all individual serious infections were reported in single subjects.

Through Week 16 in the pooled Phase 3 PsA studies and in the pooled PSO3001 and PSO3002 studies, there were no reports of TB or opportunistic infections.

Injection-site Reactions

Through Week 16, the proportions of subjects reporting ISRs were low in the pooled Phase 3 PsA studies as well as in the pooled PSO3001 and PSO3002 studies. In the pooled Phase 3 PsA studies through Week 16, ISRs were reported in 5 (1.3%) subjects in the guselkumab 100 mg q8w group, 4 (1.1%) subjects in the guselkumab 100 mg q4w group, and no subjects in the placebo group. In the pooled PSO3001 and PSO3002 studies through Week 16, ISRs were reported in 37 (4.5%) subjects in the guselkumab q8w group and 13 (3.1%) subjects in the placebo group. Through Week 16 in the pooled Phase 3 PsA studies, as well as in the pooled PSO3001 and PSO3002 studies, the most frequently reported ISR was injection site erythema.

Through Week 16 in the pooled Phase 3 PsA studies and the pooled PSO3001 and PSO3002 studies, all subjects with guselkumab ISRs reported ISRs of mild intensity with the exception of 1 subject in the guselkumab q4w group in the pooled Phase 3 PsA studies who reported 3 ISRs of moderate intensity. This subject discontinued study agent after the first dose due to injection site erythema, injection site swelling, and injection site warmth.

Malignancies

In the pooled Phase 3 PsA studies, no subjects reported NMSC and malignancies other than NMSC, were reported in 2 subjects in the guselkumab 100 mg q8w group (malignant melanoma in situ and plasma cell myeloma) and 1 subject in the placebo group (clear cell renal cell carcinoma).

When PSO3001 and PSO3002 were pooled through Week 16, NMSC was reported in 1 subject in the guselkumab group (basal cell carcinoma) and no other malignancies were reported in guselkumab- or placebo-treated subjects.

MACE

In the pooled Phase 3 PsA studies through Week 24, there was 1 report of MACE in a subject treated with guselkumab and 1 report of MACE in a subject who received only placebo. In the pooled PSO3001 and PSO3002 studies through Week 16, MACE was reported in 1 subject treated with guselkumab.

Anaphylactic and Serum Sickness Reactions

In the pooled Phase 3 PsA studies through Week 24 and in the pooled PSO3001 and PSO3002 studies through Week 16 there were no reports of anaphylaxis or serum sickness reactions.

Relationship Between Antibodies to Guselkumab and Safety in Psoriatic Arthritis

The overall incidence of antibodies to guselkumab through Week 24 was low (2.0%, 15 of 744 subjects) in subjects with PsA. The highest titers of antibodies to guselkumab observed were 1:5,120. In addition, the incidence of antibodies to guselkumab through Week 24 was comparable between the 2 dose groups (100 mg q8w: 1.6% [6 of 373 subjects]; 100 mg q4w: 2.4% [9 of 371 subjects]).

Only 1 of the 15 subjects (6.7%) who was positive for antibodies to guselkumab was also positive for neutralizing antibodies (NAbs) to guselkumab. In PSA3001, 1 of the 5 subjects who was positive for antibodies to guselkumab was positive for NAbs to guselkumab. In PSA3002, none of the 10 subjects who were positive for antibodies to guselkumab status were positive for NAbs to guselkumab.

For subjects who were positive for antibodies to guselkumab, 9 of 15 (60%) subjects had 1 or more AEs through Week 24. For subjects who were negative for antibodies to guselkumab, 354 of 729 (48.6%) subjects had 1 or more AEs through Week 24.

None of the 15 subjects who were positive for antibodies to guselkumab had an ISR through Week 24, while 7 (1.0%) of the 729 subjects who were negative for antibodies to guselkumab had at least one ISR. No events of hypersensitivity (Type 1) were reported through Week 24 in the Phase 3 PsA studies.

Post marketing experience

Post-marketing information has been accruing since the first approval of guselkumab for the treatment of adult patients with moderate-to-severe plaque psoriasis by the United States Food and Drug Administration on 13 July 2017. As of 12 July 2019, guselkumab is approved in the European Union, the United States, Japan, Canada, and many other countries worldwide.

The estimated cumulative global exposure to guselkumab from launch through 30 June 2019 is 34,505 person-years. The evaluation of post-marketing data is part of the Sponsor's comprehensive safety surveillance program, which also includes review of data from ongoing clinical studies and registries. Periodic Safety Update Reports generated for guselkumab reflect ongoing post marketing safety surveillance, as well as assessments of all important identified and potential risks.

The cutoff date for post-marketing data in this SCS is 12 July 2019, which coincides with the most recent Periodic Safety Update Report cutoff date. No new ADRs were identified in the most recent Periodic Safety Update Report. Guselkumab continues to have a favorable benefit-risk profile for the treatment of adult patients with moderate-to-severe plaque psoriasis. The Sponsor will continue to monitor the safety profile of guselkumab and report the safety findings as appropriate. There is no post marketing data for the Q4W regimen

2.5.1. Discussion on clinical safety

The approved dose of guselkumab for the treatment of plaque psoriasis is 100 mg administered subcutaneously (SC) at Week 0, Week 4, and every 8 weeks (q8w) thereafter. This was based primarily on two large, Phase 3, placebo-controlled clinical studies (PSO3001 and PSO3002). The overall safety profile of guselkumab was in line with compounds in the similar therapeutic class interfering with the IL-pathway in psoriasis. In general, the incidence of adverse events was low, mostly similar to placebo, similar to or more favourable than the active comparator adalimumab or ustekinumab and they were mainly mild in severity. The long-term extension data from the Phase 3 psoriasis studies through 3 years demonstrated that the 3-year safety profile was consistent with the 1-year safety data reported in the original psoriasis marketing application.

The clinical development program of guselkumab for the treatment of active psoriatic arthritis (PsA) includes a completed global Phase 2 study (PSA2001) and 2 global Phase 3 studies (PSA3001 and PSA3002). Through the data cut (01 May 2019), a total of 1,229 subjects with active PsA were exposed to guselkumab across the Phase 2 (PSA2001) and Phase 3 PsA studies (PSA3001 and PSA3002), including 1,093 (88.9%) subjects treated for at least 6 months and 588 (47.8%) subjects treated for at least 1 year.

The safety profile in the PsA population was generally comparable with that established in the psoriasis population.

The overall frequency of AEs was similar in the guselkumab q8w, guselkumab q4w, and placebo groups through Week 24. The most common AEs in subjects exposed to guselkumab were in the Infections and infestations SOC; and the frequencies of AEs in this SOC were generally comparable across the guselkumab and placebo groups with no dose dependency. Through Week 24, the most frequently reported AEs in subjects treated with guselkumab were ALT increased, nasopharyngitis, AST increased, and URTI. AST increased, bronchitis, headache, respiratory tract infection, injection site erythema and oropharyngeal pain were reported more frequently in the guselkumab groups compared with the placebo group. Neutrophil count decreased, hyperuricaemia, and hepatic steatosis were reported more frequently in the guselkumab q4w group compared with the q8w group. Respiratory tract infection (very common), transaminases increased (common), and neutrophil count decreased (uncommon) were identified as a new ADRs for guselkumab and added to 4.8 of the SmPC. Furthermore the frequencies of Urticaria, Tinea infections, Gastroenteritis and Herpes simplex infections were updated in their frequencies from common to uncommon.

Through the data cut, both the overall frequency of AEs and the frequency of AEs in the Infections and infestations SOC were similar in the guselkumab q8w and guselkumab q4w groups. Through the data cut, there was no evidence for an increase in the overall follow-up adjusted AE rates in subjects treated with guselkumab q8w or guselkumab q4w when compared with data through Week 24. The most frequently reported AEs in subjects treated with guselkumab were nasopharyngitis, ALT increased, URTI, and AST increased.

The overall frequency of AEs of infections was similar in the guselkumab q8w, guselkumab q4w, and placebo groups through Week 24 and in the guselkumab q8w and guselkumab q4w groups through the data cut. Serious infections occurred infrequently in all treatment groups through the data cut and all AEs of serious infection were reported in single subjects. Through the data cut, there was no evidence for an increase in the overall follow-up adjusted rates of AEs of infections or serious infections in subjects treated when compared with data through Week 24. There were no reports of active TB or an opportunistic infection in any of the guselkumab-treated subjects.

In the two phase III psoriatic arthritis clinical studies through Week 24, the number of subjects that reported 1 or more injection site reactions was low and slightly higher in the Tremfya groups than in the placebo group; 5 (1.3%) subjects in the Tremfya q8w group, 4 (1.1%) subjects in the Tremfya q4w group, and 1 (0.3%) subject in the placebo group. One subject discontinued Tremfya due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies. This information has been added to the SmPC.Most ISRs were of mild intensity, there were no serious ISRs, 2 subjects in the guselkumab q4w group discontinued study agent due to ISRs of moderate intensity.

The data from the pooled Phase 3 PsA studies demonstrate a small number of malignancies, with corresponding rates similar to what would be expected in the general population.

There was no evidence for an increase in the rate of subjects reporting MACE in the pooled Phase 3 PsA studies.

There was no evidence for an increase in the reporting rate of SIB over time through the data cut and the follow-up adjusted number of subjects reporting SIB in both guselkumab groups remained lower than the placebo group through Week 24.

No cases of anaphylaxis or serum sickness reaction were reported through the data cut in PSA3001 and PSA3002.

Through Week 24, there were no reports of new onset or exacerbation of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, in guselkumab-treated subjects. More long-term data will become available when final data from clinical study PSA3002 will be submitted as defined in the RMP .

No deaths were reported in any of the guselkumab treated groups.

The overall follow-up adjusted SAE rates in the guselkumab q8w, guselkumab q4w, and guselkumab q4w combined groups were low and similar across groups. Through the data cut, there was no evidence for an increase in the overall follow-up adjusted SAE rates in subjects treated with guselkumab q8w or guselkumab q4w when compared with data through Week 24. Most SAEs reported in subjects exposed to guselkumab were reported in single subjects.

Overall, any abnormal hematology laboratory parameters of Grade 2 or higher were infrequent (≤3.4% in the combined guselkumab groups). Through Week 24 and the data cut decreases in neutrophil, WBC and platelet counts were observed in the guselkumab groups. From baseline to Week 24, a shift in neutrophil count from within the normal reference range to below the normal reference range was reported in a greater proportion of subjects in the guselkumab groups compared with the placebo group. A numerical trend of a greater mean reduction from baseline in neutrophil and WBC counts in the guselkumab groups compared with the placebo group was observed over time through Week 24. Through the data cut, the mean change from baseline in neutrophil and WBC counts was similar between the guselkumab q8w and q4w groups. A greater frequency of decreases in neutrophil counts and WBC counts was observed with longer duration of exposure through 1 year. No Grade 3 or higher WBC count decrease was observed through 1 year. Grade ≥2 neutrophil count decreases and Grade 2 WBC count decreases in guselkumab-treated subjects were generally not associated with infections. Mean values for neutrophil counts and WBC counts in the guselkumab q8w and q4w groups did not further decrease from Week 24 through 1 year of treatment. The majority of cases of neutrophil and WBC count decreases were transient and reversible, resolved spontaneously without treatment and were not associated with infections. At the Week 24 assessment neutropenia was not the reason of discontinuation of study agent administration but at Week 44 one case is mentioned. The number of neutrophils decreased, although not seriously during the psoriasis clinical studies as well. 'Neutrophil count decreased' is considered as a new adverse drug reaction and reflected in 4.8 of the SmPC. The clinical consequences of neutropenia is addressed in the RMP under the important potential risk: "serious infection".

A numerical trend of a greater mean reduction from baseline in platelets in the guselkumab groups compared with the placebo group was observed over time through Week 24. Through the data cut, the mean decrease from baseline in platelet counts was comparable in the guselkumab q8w and q4w groups. The proportions of subjects with Grade 1 or higher decreases in platelet counts were low and comparable across the guselkumab q4w, guselkumab q8w, and placebo groups. Among all guselkumab-treated subjects, at most timepoints through the data cut the mean decrease from baseline in platelet count was <25 x 109/L; the mean decrease was slightly greater at later timepoints (ie, Week 84 and later) that included fewer subjects. Compared to the proportion of subjects with a shift in platelet count from within/above reference range at baseline to below reference range post baseline in the placebo-controlled period, as expected, a greater proportion of subjects with shifts was observed with longer duration of

exposure through 1 year. There was no further decrease of mean platelet counts from Week 24 through 1 year. The decreases in platelet counts were transient, resolved spontaneously without treatment, did not lead to study agent interruption or discontinuation, and were not associated with bleeding events. Mean platelet counts appeared to plateau 12 to 16 weeks after first treatment of guselkumab at Week 0 and were consistent with expected changes due to a decrease in inflammatory response following anti-inflammatory treatment.

Overall, there were no clinically significant trends for chemistry laboratory parameters other than Increases in ALT and AST, that were observed with a higher frequency in the guselkumab groups compared with the placebo group. Through Week 24, Grade 2 or higher increases in ALT and AST were reported infrequently (<3%) and were reported more frequently in the guselkumab q4w group compared with the guselkumab q8w and placebo groups. Through the data cut, Grade 2 increases in ALT and Grade 2 and Grade 3 increases in AST were reported more frequently in the q4w group compared with the q8w group giving the impression of being dose related. Among all guselkumab-treated subjects, the mean change from baseline in ALT was generally an increase of approximately 1 to 3 U/L at all timepoints through the data cut; the mean increase was slightly greater at later timepoints (ie, Week 68 and later). It is noted that the increases from baseline were generally transient without an apparent pattern in onset, resolved spontaneously, and did not result in study agent interruptions or discontinuations except in 3 subjects (not related), and were generally not associated with clinically significant increases in bilirubin. Through 1 year, most post-baseline increases in ALT and AST were Grade 1 and the proportions of subjects with Grade 1 or higher post-baseline increases in ALT were higher in the guselkumab q4w (46.9%) group compared with the q8w group (36.2%). The proportions of subjects with Grade 1 or higher post-baseline increases in AST were also slightly higher in the guselkumab q4w (33.2%) group compared with the q8w group (26.3%). A higher frequency was observed with the longer duration of exposure through 1 year. No events that satisfied the criteria for Hy's Law (total bilirubin >2×ULN and either ALT or AST ≥3×ULN) in guselkumab-treated subjects through 1 year were reported.

AEs reported in the Hepatobiliary disorders SOC were comparable between the guselkumab q4w (3.5%) and q8w (2.7%) groups. The majority of AEs reported through 1 year were preferred terms (PTs) related to hepatic steatosis for both the q4w (2.7%) and q8w (1.3%) groups. The majority of the hepatic steatosis events was reported as mild and considered not related to study treatment by the investigator and confounded by several other factors such as obesity, use of other hepatotoxic concomitant medications (ie, MTX, NSAIDs), and reported alcohol use. Through 1 year, 3 subjects in the guselkumab q4w group reported PTs of Drug-induced liver injury (DILI), Hepatitis toxic, and Hepatocellular injury (one subject each) and causality was assessed as related to the concomitant anti-TB therapy in all 3 subjects. A comprehensive review of the guselkumab safety database, performed for the evaluation of a potential DILI case reported in the Crohn's disease study, did not identify any concerns of DILI in guselkumab-treated subjects either in clinical studies across all indications or in postmarketing experience. In subjects with baseline MTX use, Grade 1 or higher increases in ALT were more frequent than in subjects without baseline MTX use. In subjects with baseline use of MTX and NSAIDs, Grade 1 or higher increases in ALT and AST were reported more frequently in the guselkumab q4w group compared with the q8w group and were comparable to the frequency of elevations seen in subjects with baseline use of MTX alone. As in the overall population, the majority of these increases was Grade 1 and the frequencies of Grade 2 or higher increases remained low through 1 year.

Emergency Safety Issue of DILI observed in GALAXI study was a serious liver injury event occurring after i.v. exposure of 1200 mg guselkumab dose, without co-administration of other liver-damaging medicinal products, it was a single event observed in a Crohn's disease patient.

In PSO studies, slight tendencies of transaminase increases were observed in guselkumab 100 mg sc at Week 0, 4 and every 8 weeks thereafter even in long-term setting.

In the RA study, there was no dose-related effect on shifts in ALT or AST from below or within normal range to above normal range in guselkumab-treated subjects. There was also no dose-related increase in frequencies in guselkumab-treated subjects with .Grade 1 increases in ALT or AST.

The PRAC accepted the Applicant's position that no additional risk minimalisation measures should be included into RMP.

Nevertheless, slight increases of frequencies of ALT and AST elevations in guselkumab groups in PSO studies vs placebo, the difference in frequencies of transaminase increases in PsA and the DILI event after high i.v. dose of guselkumab in a Crohn's disease patient refer for possibility of dose dependence of incidence of transaminase elevation AEs and an elevated risk of liver injury.

Thus information on increased transaminases has been added to 4.8 and a warning on liver function monitoring in patients receiving Q4W therapy was added to 4.4 of the SmPC at the CHMP's request.

Overall through Week 24 and through the data cut, no trends were observed with regard to differences between the guselkumab and placebo groups or between the guselkumab q8w and q4w groups in the proportions of subjects with AEs, SAEs, AEs leading to discontinuation of study agent, infections, or serious infections when evaluated by intrinsic factors related to baseline demographic or disease characteristics or by extrinsic factors of geographic region.

In subjects using corticosteroids at baseline, SAEs and infections were seen in greater proportions of subjects in the guselkumab q4w group compared with the q8w group through Week 24. Through 1 year, SAEs were more frequent in the guselkumab q4w group compared with the q8w group although it should be noted that there were few events, and the majority of these events was not related to infection. The rates of infections and serious infections in subjects using corticosteroids at baseline were similar between the guselkumab q4w and q8w groups through 1 year.

The differences observed at Week 24 in the frequency of AEs and infections between the guselkumab q4w and q8w groups in subjects using non-biologic DMARDs at baseline were no longer present at 1 year, and the frequency of serious infections in subjects using non-biologic DMARDs at baseline was also comparable between the guselkumab q4w and q8w groups at 1 year.

In subjects with prior anti-TNFα exposure, the increase in AEs and infections (but not serious infections) in the guselkumab q4w group compared with the q8w group through 1 year was likely related to the small number of subjects in this subgroup.

Discontinuation of treatment with guselkumab q8w and guselkumab q4w for an AE(s) was infrequent. Through Week 24, as well as through the data cut the overall rates of AEs leading to discontinuation of study agent per 100 subject-years of follow up were higher for the guselkumab q4w treated group than for the guselkumab q8w and placebo groups.

There was no apparent association between the development of antibodies to guselkumab and the incidence of AEs. However, the small number of subjects who were positive for antibodies to guselkumab limits a definitive conclusion regarding the impact of antibodies to guselkumab on the incidence of AEs.

2.5.2. Conclusions on clinical safety

The safety profile in the PsA population was generally comparable with that established in the psoriasis population and data on long term safety will be complemented post authorisation with final results of study PSA3002 which is defined as a category 3 study in the RMP. Based on the review of the pooled Phase 3 PsA studies through Week 24, additional ADRs of Respiratory tract infection, Transaminases increased, and Neutrophil count decreased were identified and added to the SmPC. Adverse event profile was rather mild, guselkumab can be considered well-tolerated.

There was a marginal trend with increases in transaminases slightly higher in the guselkumab q4w group compared with the q8w group, the numbers are low. However, a consistent safety profile with the majority of subjects experiencing increases in transaminases of Grade 1 increases, no events that satisfied the criteria for Hy's Law (total bilirubin >2×ULN and either ALT or AST ≥3×ULN) in guselkumab-treated subjects through 1 year were reported. Increase of transaminases was added as a new ADR in 4.8 of the SmPC as well as differences observed in liver function tests between the q4w and q8w dose. Furthermore cautionary statements were added in 4.4 of the SmPC including the recommendation to evaluate liver enzymes at baseline and thereafter according to routine patient management when prescribing Tremfya q4w in psoriatic arthritis and to interrupt treatment with Tremfya if increases in ALT or AST are observed and drug-induced liver injury is suspected until this diagnosis is excluded..

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 MAH submitted an updated RMP version 6.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.1 with the following content:

Safety concerns

Important **identified risks: None**

Important potential risks:

- Serious infection
- Malignancy
- Serum sickness
- Major adverse cardiovascular events (MACE).

Missing information:

- Exposure during pregnancy
- Use in patients ≥65 years of age
- Long-term safety of guselkumab

Ongoing and Planned Additional Pharmacovigilance Activities

Trial Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
CNTO1959PSO3001 Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Interim report Final report	December 2016 May 2021
CNTO1959PSO3002 Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Interim report Final report	December 2016 June 2021
CNTO1959PSA3002 Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Interim report Final report	October 2019 December 2021
Registry C0168Z03 Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Interim report Final report	4Q 2025 4Q 2030

Trial Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
PsoBEST Registry (CNTO1959PSO4001) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Interim report	After enrollment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year)
			Final report	4Q 2030
Electronic Administrative Health Claims Databases Review (PCSIMM001324) Ongoing	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes in infants up to 1 year of age	• Exposure during pregnancy	Interim report	4Q 2025
			Final report	4Q 2030

Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infection	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* *SmPC Section 4.3 (Contraindications)* *SmPC Section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet Section 2* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *TFUQ* **Additional pharmacovigilance activities:** *CNTO1959PSO3001* Final report: May 2021 *CNTO1959PSO3002* Final report: June 2021 *CNTO1959PSA3002* Final report: December 2021 *Registry C0168Z03* Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030
Malignancy	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *TFUQ* **Additional pharmacovigilance activities:** *CNTO1959PSO3001* Final report: May 2021 *CNTO1959PSO3002* Final report: June 2021 *CNTO1959PSA3002* Final report: December 2021 *Registry C0168Z03*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030
Serum sickness	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* *SmPC Section 4.3 (Contraindications)* *SmPC Section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet Section 2* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *TFUQ* **Additional pharmacovigilance activities:** *CNTO1959PSO3001* Final report: May 2021 *CNTO1959PSO3002* Final report: June 2021 *CNTO1959PSA3002* Final report: December 2021 *Registry C0168Z03* Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Major adverse cardiovascular events (MACE)	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *TFUQ* **Additional pharmacovigilance activities:** *CNTO1959PSO3001* Final report: May 2021 *CNTO1959PSO3002* Final report: June 2021 *CNTO1959PSA3002* Final report: December 2021 *Registry C0168Z03* Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030
Exposure during pregnancy	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* *SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) and Package Leaflet Section 2* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Follow-up of reported pregnancies* **Additional pharmacovigilance activities:** *Registry C0168Z03* Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030 *Electronic Administrative Health Claims Databases Review (PCSIMM001324)* Final report: 4Q 2030
Use in patients ≥65 years of age	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None.* **Additional pharmacovigilance activities:** *Registry C0168Z03* Final report: 4Q 2030

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	No risk minimization measures	*PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030
Long-term safety of guselkumab	**Routine risk minimization measures:** *SmPC Section 4.2 (Posology and Method of Administration)* **Additional risk minimization measures:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *None.* **Additional pharmacovigilance activities:** *CNTO1959PSO3001* Final report: May 2021 *CNTO1959PSO3002* Final report: June 2021 *CNTO1959PSA3002* Final report: December 2021 *Registry C0168Z03* Final report: 4Q 2030 *PsoBEST Registry (CNTO1959PSO4001)* Final report: 4Q 2030

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. Additionally, minor QRD changes are introduced in annex II. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Same pharmaceutical form and presentations will be used for the Psoriatic Arthritis indication as those already licensed for use in the Psoriasis indication (solution for injection in pre-filled syringe, and solution for injection in pre-filled pen).

PsA patient population is not considered different from psoriasis patient population in terms of visual and reading capabilities

Only minor changes are proposed in Tremfya PL, its design and layout remain unchanged.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriatic arthritis is a chronic inflammatory arthropathy of the peripheral and axial joints associated with psoriasis. The estimated prevalence of PsA in the general population varies from 0.02% to 1.0% across the world; in patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. PsA impacts the joints, bone and cartilage, periarticular tissues (dactylitis), entheses, and skin, and can result in functional disability and impaired quality of life.

The severity of disease can vary substantially among patients, with some patients developing destructive arthritis leading to bony erosion and loss of joint architecture. In long-term cohort studies of patients with PsA, it has been estimated that approximately 50% to 60% of patients with PsA will not exhibit structural damage over time.

Guselkumab (Tremfya) has been approved in the EU for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

This submission presents data to support the use of guselkumab in adult patients with active psoriatic arthritis (PsA). The indication claimed is as follows:

Psoriatic arthritis
Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

3.1.2. Available therapies and unmet medical need

Anti-TNFα agents were the first biologic agents approved for the treatment of PsA. Ustekinumab, an inhibitor of IL-12/23, apremilast, an inhibitor of PDE4, secukinumab and ixekizumab, antibody directed against IL-17, were also recently approved for PsA. These therapies have greatly improved the management of patients with PsA. Unfortunately, 40% to 60% of patients treated with current therapies do not reach a minimal improvement in their joint disease (ie, ACR 20) based on clinical trial data. In addition, TNFi-exposed patients may be more resistant to treatment, as the proportion of subjects achieving an ACR 20 was lower for TNFi-exposed than in TNFi-naive subjects in trials of ustekinumab, apremilast, and secukinumab.

3.1.3. Main clinical studies

The guselkumab clinical development program for PsA includes a completed Phase 2 (CNTO1959PSA2001) and two Phase 3 (CNTO1959PSA3001 and CNTO1959PSA3002 (ongoing)) studies in adult subjects with PsA who had inadequate response to, or were intolerant of conventional therapy (ie, non biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, or nonsteroidal anti-inflammatory drugs [NSAIDs]), and/or anti-tumor necrosis factor alpha (TNFα) therapies (PSA2001 and PSA3001 only). The guselkumab 100 mg SC at Weeks 0, 4, and every 8 weeks (q8w) thereafter dose regimen was evaluated in study PSA2001. Both the guselkumab q8w and guselkumab SC 100 mg every 4 weeks (q4w) dose regimens were evaluated in studies PSA3001 and PSA3002.The MAH provided preliminary efficacy and safety data from the phase 3 studies through week 52.

The primary endpoint in theses studies, ACR 20 at week 24, is in line with the current PsA guidelines and with previous applications authorised in this condition.

The key secondary endpoints examined effects on a range of efficacy measurements such as HAQ DI, DAS 28 CRP, ACR 50, 70 effects on dactylitis and enthesitis.

The 3002 study examined effects on Mtss radiographic changes, this was an enriched population who had active disease defined by high CRP and ≥5 tender and swollen joints and had an inadequate response to DMARDs.

Additional endpoints included quality of life measurements, minimal and very low disease activity, PK exposure response relationship, antibody responses and subgroup analysis.

3.2. Favourable effects

In the 2 large placebo-controlled Phase 3 studies (PSA3001 and PSA3002), guselkumab 100 mg at Weeks 0, 4 and q8w thereafter as well as guselkumab 100 mg q4w demonstrated significant and clinically meaningful efficacy relative to placebo across multiple endpoints and subpopulations of PsA.

At the primary endpoint ACR20 response rate at Week 24 as well as at key secondary endpoints ACR50 and ACR70 response rates at Week 24 guselkumab Q4W and Q8W dosing regimens reached statistically significant therapeutic response over placebo in study PSA3001. In study PSA3002, both dosing regimens reached statistical significance at ACR20 response rate.

As for psoriasis-related endpoints, PASI75 responder rate was between 70-85% during the two Phase-3 study, PASI90, was between 50-60%.

Efficacy endpoints characterising dactylitis, enthesetis and spondylitis demonstrated improvement for both treatment regimens in PSA3001 study, and for Q4W treatment group in PSA3002 study.

According to Phase-2 study PSA2001 and the preliminary long-term data submitted with D121 responses, effect on ACR-endpoints and several other endpoints for PsA disease activity, psoriatic skin disease and joint disease progression was maintained or efficacy was even increased through Week 52.

In DISCOVER 2, inhibition of structural damage progression was measured radiographically and expressed as the mean change from baseline in the total modified van der Heijde-Sharp (vdH-S) score. At Week 24, the guselkumab q4w group demonstrated statistically significantly less radiographic progression and the guselkumab q8w group showed numerically less progression than placebo (Table 9). The observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (ie, smaller mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in subjects with both a high C-reactive protein value and high number of joints with erosions at baseline. Based on DISCOVER 2 study results, the MAH proposed a more frequent posology (100 mg s.c. every 4 weeks) for patients at high risk for joint damage according to clinical judgement. To define PsA patient subgroups who may or may not have a high risk for radiographic progression and may benefit from the q4w dosing regimen the MAH provided post-hoc analyses by relevant baseline disease characteristics which predict risk for radiographic progression in PsA, by baseline radiographic scores and performed risk factor identification via CART analysis. Radiographic results from three separate approaches all supported an incremental benefit of the guselkumab q4w dose regimen on inhibition of structural damage compared to the q8w regimen.

3.3. Uncertainties and limitations about favourable effects

The pattern of changes in the biomarker levels is consistent with the presumed mode of action of guselkumab. However, connection between the change in biomarker levels and clinical outcomes had not been shown. The PD effect on biomarkers is unquestionable but this effect does not seem directly related to clinical PsA specific clinical response (ACR20, IGA). Furthermore, no difference can be seen between the Q4W and Q8W regimens' PD effects. A plausible hypothesis that the PD effects in both cases are maximal, on the plateau however, direct experimental evidence to support this notion is lacking.

The baseline DAS28 score was identified as a covariate based on Emax, with a trend indicating that subjects with lower baseline DAS28 scores had higher ACR20/50/70 responses. This seems to be a class effect characteristic of other anti-PSA biologicals.

In the overall PsA study population, the effect of q4w dose on inhibiton of radiographic progression was higher (and significant) than with q8w dose (no- significant) at week 24. The effect of the guselkumab q8w dose regimen on inhibition of radiographic progression was higher than with q4w dose beyond Week 24 (to week 52), suggesting that the benefit of q8w dosing on radiographic endpoints increases with longer exposure. Thus, altogether, the mean change in total mvdH-S was similar in the guselkumab q4w (1.07) and q8w groups (0.97) over 1 year of treatment in the overall PsA study population. Appropriate information has been added to 5.1 of the SmPC.

The MAH explained that due to the baseline imbalance in radiographic scores, the benefit of guselkumab q4w may have been underestimated at both Week 24 compared to placebo and at Week 52 compared to guselkumab q8w dose regimen. Further data on immunogenicity and long-term safety and efficacy, in particular for higher threshold parameters and disease progression will become available with the final data on the Phase 3 study PSA3002 which is defined as a category 3 study in the RMP

3.4. Unfavourable effects

The overall safety profile of guselkumab from previously completed studies appeared in line with compounds in the similar therapeutic class interfering with the IL-pathway in psoriasis. In general, the incidence of adverse events was low, mostly similar to placebo, similar to the active comparator adalimumab or ustekinumab and they were mainly mild in severity. The long-term extension data from the Phase 3 psoriasis studies through 3 years demonstrated that the 3-year safety profile was consistent with the 1-year safety data reported in the original psoriasis marketing application.

The safety profile in the PsA population was generally comparable with that established in the psoriasis population.

Based on the review of the pooled Phase 3 PsA studies through Week 24, additional ADRs of Respiratory tract infection, Transaminases increased, and Neutrophil count decreased were identified and added to the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Longer-term safety of guselkumab in the PsA and moderate to severe plaque psoriasis population will be monitored in the ongoing studies PSA3002, PSO3001, and PSO3002, and through appropriate registries as defined as additional pharmacovigilance activities (category 3 studies) in the RMP.

Clinical haematology laboratory values assessed during the Phase 3 PsA studies show decrease in neutrophil and platelet count the decrease in blood neutrophil count was mild, transient, not associated

with infection and did not lead to discontinuation of treatment. This information was added to the SmPC and is addressed in the RMP under the potential risk “serious infection”.

In pooled phase III analyses in patients with psoriatic arthritis, 2% (n=15) of patients treated with Tremfya developed antidrug antibodies in up to 24 weeks of treatment. Of these patients, 1 patient had antibodies that were classified as neutralizing. None of these patients developed injection site reactions. Overall, the small number of patients with antidrug antibodies limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics, efficacy or safety of guselkumab in patients with psoriatic arthritis. This information has been added to the SmPC.

Possibly dose related transaminase elevations were observed: there was marginal trends with increases in transaminases slightly higher in the guselkumab q4w group compared with the q8w group, the numbers are low but appropriate information was added to 4.8 of the SmPC for the awareness of the prescriber. Guselkumab shows a consistent safety profile in PsA and PsO trials, with the majority of subjects experiencing increases in transaminases of Grade 1 increases, no events that satisfied the criteria for Hy’s Law (total bilirubin >2×ULN and either ALT or AST ≥3×ULN) in guselkumab-treated subjects through 1 year were reported. Through 1 year, 3 subjects in the guselkumab q4w group reported PTs of Drug-induced liver injury (DILI), Hepatitis toxic, and Hepatocellular injury (one subject each) and causality was assessed as related to the concomitant anti-TB therapy in all 3 subjects. A comprehensive review of the guselkumab safety database, performed for the evaluation of a potential DILI case reported in the Crohn’s disease study, did not identify any concerns of DILI in guselkumab-treated subjects either in clinical studies across all indications or in postmarketing experience. Therefore, further pharmacovigilance or risk minimisation measures are currently not warranted but the issue is to be followed up in future PSURs. Still, a higher incidence of liver dysfunction with Q4W vs Q8W regimen was observed in PsA studies through Week 24. Also, in PSO studies, slight tendencies of transaminase increases were observed in guselkumab 100 mg sc at Week 0, 4 and every 8 weeks thereafter even in long-term setting. In an ongoing RA study, however, there was no dose-related effect on shifts in ALT or AST from below or within normal range to above normal range in guselkumab-treated subjects.

Accordingly, precautionary statements were included in section 4.4 for liver function monitoring in patients receiving Q4W therapy.

3.6. Effects Table

Table 1. Effects Table for Tremfya, psoriatic arthritis (data cut-off: 14 March 2019-PSA3001, 09 March 2019 – PSA3002)

Effect	Short description	Unit	CI, p	Treatment guselkumab 100 mg s.c. q8w	Treatment guselkumab 100 mg s.c. q4w	Control placebo	Uncertainties / Strength of evidence	References
		Favourable Effects						
ACR20	% achieving response at Week 24 (primary endpoint)	N(%)	p	PSA3001 66 (52.0%) <0.001	PSA3001 76 (59.4%) <0.001	PSA3001 28 (22.2%)	PSA3001 study: imbalance in BL ACR components between the two guselkumab groups	PSA3001 PSA3002
	N (%)			PSA3002 159 (64.1%) <0.001	PSA3002 156 (63.7%) <0.001	PSA3002 81(32.9%)	subjects with lower baseline DAS28 scores had higher ACR20/50/70 responses. It is not clear this	

Effect	Short description	Unit CI, p	Treatment guselkumab 100 mg s.c. q8w	Treatment guselkumab 100 mg s.c. q4w	Control placebo	Uncertainties / Strength of evidence	References
						inflammation dependent effect is a particular feature of guselkumab	
ACR50	% achieving response at Week 24 (primary endpoint)	N(%) p	PSA3001 38 (29.9%) <0.001	PSA3001 46 (35.9%) <0.001	PSA3001 11(8.7%)		
			PSA3002 78(31.5%) <0.001	PSA3002 81 (33.1%) <0.001	PSA3002 35(14.2%)		
DAS28(CRP)	Calculated from TJC28, SJC28 CRP and PtGA	LSMean 95% CI p	PSA3001 -1.43 (-1.61- -1.24) <0.001	PSA3001 -1.61 (-1.80- -1.42) <0.001	PSA3001 -0.70 (-0.89- -0.51)	Efficacy and safety of two guselkumab dosing regimens on PsA were studied in three placebo-controlled DB clinical studies (one F-2 and two F-3 studies) Both Guselkumab doses had significant effect on the primary endpoint and on all but one secondary endpoints of these studies. Guselkumab 100 mg Q8W dosis did not reached significance on key secondary endpoint of change from BL of mean modified vdH-S Score. Therapeutic effect of both guselkumab doses was consistent across various BL characteristics, demography, BL disease characteristics and prior/concomitant medication subgroups.	
			PSA3002 -1.62 (-1.80- -1.42) <0.001	PSA3002 -1.59 (-1.72- -1.45) <0.001	PSA3002 -0.97 (-1.11- -0.84) <0.001		
PASI75	75% reduction on PASI score at week 24	N (%) p value	62 (75.6%)	PSA3001 77 (86.5%)	PSA3001 11 (14.1%)	Lower PASI responses compared to guselkumab PSO studies – reason unknown at the moment.	
			139 (79.0%)	144 (78.3%)	PSA3002 42 (23.0%)		
PASI90	90% reduction on PASI score at week 24	N (%) p value	41 (50.0%)	56 (62.9%)	PSA3001 9 (11.5%)		
	N (%) p value		121 (68.8%)	112 (60.9%)	PSA3002 18 (9.8%)		
vdH-SS						The claimed statistically significant effect on the secondary endpoint vdH-S scores is dubious. The vdH-S score distribution plots are	

Effect	Short description	Unit CI, p	Treatment guselkumab 100 mg s.c. q8w	Treatment guselkumab 100 mg s.c. q4w	Control placebo	Uncertainties / Strength of evidence	References
						not supporting the assumptions of the underlying statistical analysis and further justification is needed.	
HAQ-DI – change from BL at Week 24	Assesses the degree of difficulty a person had in accomplishing tasks in 8 functional areas. Responses in each functional area were scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area	LSMean 95% CI	PSA3001 -0.3225 (-0.4082- -0.2369) <0.001 PSA3002 -0.4617 <0.001	PSA3001 -0.3968 (-0.4825- -0.3112) <0.001 PSA3002 -0.4282 <0.001	PSA3001 -0.0743 (-0.1605-0.0119) <0.001 PSA3002 -0.1300 <0.001		
Unfavourable Effects							
AEs	Subjects with any AEs,	%	48,5%	48,8%	47,3%	comparison to previous study results suggest comparable safety	PSA3001 PSA3002
SAEs	Subjects with SAEs	%	1,9%	2,1%	3,2%	comparison to previous study results suggest comparable safety	PSA3001 PSA3002
Neutrophil count decreased		% /L	7,2% -0,7x10^9/L	7.8% -0,6x10^9/L	4,3% -0,2x10^9/L	Applicant is asked to discuss the effect of long term guselkumab exposure.	PSA3001 PSA3002
Platelet count decreased		% /L	2,6% -21,7x10^9/L	1,6% -21,0x10^9/L	1,6% -3,4x10^9/L	Possible connection with treatment, Applicant is asked to discuss.	PSA3001 PSA3002
AST increased		% U/L	20,9% 3,7U/L	24,8% 2,4U/L	21,7% 1,4U/L	Applicant is requested to further discuss possible liver injury and	PSA3001 PSA3002
ALT increased		% U/L	30,1% 3,5U/L	38,8% 2,9U/L	32,3% 0,8U/L		PSA3001 PSA3002

Effect	Short description	UnitCI, p	Treatment guselkumab 100 mg s.c. q8w	Treatment guselkumab 100 mg s.c. q4w	Control placebo	Uncertainties / Strength of evidence	References
						possible background of action	
Infections		%	19,5%	21,4%	20,7%	comparison to previous study results suggest comparable safety	PSA3001 PSA3002

Table 2. Abbreviations: AE adverse event; SAE serious adverse event; ALT alanine aminotransferase; AST aspartate aminotransferase; q4w every 4 weeks; q8w every 8 weeks

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Guselkumab treatment showed benefits over placebo for the treatment of the 3 major manifestations of psoriatic disease (joint, soft tissue and skin), and provided improvement of physical function and health-related quality of life in adults with active psoriatic arthritis. Both dosing regimens (q4w and q8w) reached statistical significance at ACR20 response rate. According to Phase-2 study PSA2001 and preliminary data through 1 year from the Phase 3 PsA trials, the favourable effects were maintained to Week 52.

Safety data through the data cut includes long-term safety data from 588 subjects with PsA subjects in the Phase 2 (70 subjects) and two Phase 3 (518 subjects) studies who were treated with guselkumab 100 mg q8w or q4w continuously for at least 1 year and no specific safety concerns were observed with respect to long-term safety. Longer-term safety data (through 3 years of treatment) available from the ongoing clinical studies of guselkumab in moderate to severe plaque psoriasis (PSO3001 and PSO3002), along with more than 2 years of postmarketing safety data, show that in overall, the benefit-risk profile remains favorable since the approval of guselkumab for plaque psoriasis. Additional ADRs of Respiratory tract infection, Transaminases increased, and Neutrophil count decreased were identified in PsA trials and added to the SmPC.
A higher incidence of liver dysfunction with Q4W vs Q8W regimen was observed in PsA studies through Week 24. Also, in PSO studies, slight tendencies of transaminase increases were observed in guselkumab 100 mg sc at Week 0, 4 and every 8 weeks thereafter even in long-term setting. In an ongoing RA study, however, there was no dose-related effect on shifts in ALT or AST from below or within normal range to above normal range in guselkumab-treated subjects. The information on liver dysfunction and monitoring included in the SmPC 4.4. and 4.8 for the attention of the prescriber is considered acceptable by the CHMP.

3.7.2. Balance of benefits and risks

Guselkumab may be administered alone or in combination with a non-biologic DMARD (eg, methotrexate). The Phase 3 studies PSA3001 and PSA3002 demonstrated that both guselkumab 100 mg SC q8w and q4w dose regimens are effective in improvement in the joint, soft tissue and skin

manifestations of active PsA over time through the 24-week observation period for subjects with active PsA.

Based on baseline number of joints with erosion and CRP data, the applicant provided a post-hoc analysis on the identification of the patient subpopulation gaining a clinically relevant therapeutic benefit from the Q4W dosing regimen. It is agreed that in some patients with higher risk of joint damage a deeper suppression of the disease activity as well as a need to control disease activity as soon as possible is required. While the activity of q8w regimen demonstrates efficacy beyond 24 weeks to week 52 (Discover-2) this may not be sufficient in some patients with highly active PsA who are at risk of joint erosion, therefore allowing both a q4w and q8w posology can provide more therapeutic options for patients depending on their circumstances. To guide clinicians to judge which patients need higher dose, further information to the product information is included in Section 5.1.

With regards to safety in general, the frequency and character of AEs, SAEs and AEs leading to discontinuation are comparable between the q8w and q4w dosing regimens and a dose effect is not apparent in the overall safety profile. Increases in transaminases from baseline were noted, which were slightly higher in the guselkumab q4w group compared with the q8w group but the numbers are low. Overall the increases were generally transient without an apparent pattern in onset, resolved spontaneously, did not result in study agent discontinuation and were generally not associated with clinically significant increases in bilirubin. There were no cases that met Hy's Law criteria. While additional data will be gathered post approval as per pharmacovigilance plan potential increases in liver parameters are considered manageable for specialists, with frequent liver monitoring as described in the SmPC. The long-term safety data on the higher dose is limited. However, this limited data does not suggest an overall worse safety profile of the q4w dose regimen compared to the q8w does regimen. The benefit-risk balance of guselkumab in PsA is positive for both q4w and q8w dose regimens.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Tremfya alone or in combination with methotrexate (MTX) indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy 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, II and IIIB

Extension of indication to include a new indication for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. Consequently sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are proposed to be updated. The Package leaflet is proposed to be updated in accordance. Version 5.1 of the RMP has also been submitted. Furthermore, minor QRD changes are introduced in annex II.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

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

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Tremfya-H-C-004271-II-0017'