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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ilumetri

International non-proprietary name: tildrakizumab

Procedure No. EMEA/H/C/004514/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
AET	Analytical Evaluation Threshold
AFS	Atomic Fluorescence Spectrometry
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APG	Acidic Peak Group
ASTM	American Society for Testing and Materials
BDS	Bulk Drug Substance
BPG	Basic Peak Group
C1q	Complement Component 1q
CAD	Charged Aerosol Detection
CCI	Container closure integrity
CCS	Container Closure System
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary Electrophoresis sodium dodecyl sulfate
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
CGE	Capillary Gel Electrophoresis
CI	Confidence interval
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRP	C-reactive protein
CSR	Clinical Study Report
CV	Variation Coefficient
DLQI	Dermatology Life Quality Index
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
DTL	Drug tolerance level
ELISA	Enzyme-linked immunosorbent assay
EPC	End-of-production cells
EQ-5D	European Quality of Life 5 Dimensions
EU	Endotoxin Unit
FAS	Full Analysis Set
FBS	Foetal Bovine Serum
Fc	Fragment Crystallisable
FcRn	Fc receptors
Fcγ	IgG regulated Fc
FDA	Food and Drug Administration
FMEA	Failure Mode Effect Analysis
FSS	formal stability studies
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practise
HAQ	Health Assessment Questionnaire
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Heavy Chain
HCP	Healthcare Professional
HCP-EIA	Host Cell Protein enzyme immuno assay
HCV	Hepatitis C virus
HIC	Hydrophobic Interaction Chromatography
HMW	High Molecular Weight
HP SEC	High Pressure Size Exclusion Chromatography
HP-IEX	High-Performance Ion-Exchange Chromatography
HPLC	High Pressure Liquid Chromatography
HP-SEC	High-Performance size exclusion chromatography

HS-GC	Head Space-Gas Chromatography
ICH	International Council for Harmonisation
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
IFU	Instruction for Use
IL	Interleukin
IL-23R	Interleukin-23 receptor
IPC	In-process Control
ISO	International Organisation of Standardization
IUD	Intrauterine device
KOP	Key Operational Parameter
KPA	Key Process Attribute
LC	Light Chain
LER	Low Endotoxin Recovery
LMW	Low Molecular Weight
LOQ	Limit of Quantitation
LTBI	Latent tuberculosis infection
LV	Left ventricular
MACE	Major adverse cardiovascular events
MCB	Master Cell Bank
MFI	Mirco-Flow Imaging
MMC	Multi-mode chromatography
MS	Mass Spectroscopy
MSB	Master Seed Bank
n.a.	Not applicable
N/A	Not available
NLT	Not less than
NMT	No more than
NOR	Normal Operating Range
NR	Non-responders
NSAID	Nonsteroidal anti-inflammatory drug
NVOC	Non-Volatile Organic Compounds
OFAT	one-factor-at-a-time
OOE	Out of expectations
OQ	Operational Qualification
PAR	Proven Acceptable Range
PASI	Psoriasis Area and Severity Index
PCS	Process Characterisation Studies
PDE	Permitted Daily Exposure
PDI	Polydispersity Index
PDL	Population Doubling Levels
PFS	Pre-filled Syringe
PGA	Physician's Global Assessment
Ph. Eur.	European Pharmacopoeia
PODP	Parenteral and Ophthalmic Drug Products
PP	Per-Protocol
PPQ	Process Performance Qualification
PQ	Performance Qualification
PQRI	Product Quality Research Institute
Protein A-EIA	protein A-enzyme Immunoassay
PS80	Polysorbate 80
PTFE	Polytetrafluoroethylene
PVDF	Poly Vinyl Di Fluoride
QA	Quality Attributes
qPCR	quantitative polymerase chain reaction
QT	Qualification Threshold
QTPP	Quality Target Product Profile
RABS	Restricted Access Barrier Systems
RH	Relative humidity
RLCA	Response Level Correlation Assay
RP-HPLC	Revers Phase high-performance liquid chromatography
Rpm	Revolutions Per Minute
RT	Room temperature

SAP	Statistical Analysis Plan
SbVP	Sub-visible Particle
SC	Subcutaneously
SCT	Safety Concern Threshold
SD	Standard Deviation
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SF-36	Short Form (36) Health Survey
SOC	System organ class
SVOC	Semi-Volatile Organic Compounds
Tm	Melting Temperature
TNF	Tumor Necrosis Factor
TSE	Transmissible spongiform encephalopathies
UF/DF	Ultrafiltration / Diafiltration
ULN	Upper limit of normal
UP SEC	Ultra Pressure Size Exclusion Chromatography
USP	United States Pharmacopeia
UV	Ultraviolet
VI	Visual Inspection
VOC	Volatile Organic Compounds
WBC	White blood cell
WCB	Working Cell Bank
WFI	Water For Injection
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall S.A submitted on 6 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Ilumetri, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication "Ilumya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy." The tradename Ilumya was changed during the assessment to Ilumetri.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0058/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0058/2014 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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance tildrakizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2165/1/2011/III	21 July 2011	quality, non-clinical and clinical
EMEA/H/SA/2165/1/FU/1/2012/III	24 May 2012	quality, non-clinical and clinical

1.2. Steps taken for the assessment of the product

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

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

The application was received by the EMA on	6 March 2017
The procedure started on	23 March 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 June 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 June 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 June 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 March 2018
The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– Two triggered GCP inspections were performed at 6 sites (clinical investigators, sponsor and CROs) in Germany, Australia and the United States, between 11 September 2017 and 2 February 2018. The outcome of the inspections carried out was issued on	13 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	7 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ilumetri on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The company applied for the following indication: treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

2.1.2. Epidemiology

Psoriasis manifests in a wide range of severities, affecting 2 to 3% of the general population with significant variation by geographic location and age. The prevalence of psoriasis varies in the EU from 0.6% to 8.5.

2.1.3. Aetiology, pathogenesis and Clinical presentation

Psoriasis is a chronic, immune-mediated inflammatory disease characterized by the hyper proliferation of keratinocytes and skin-infiltrating T-lymphocytes that overexpress pro-inflammatory mediators. The disease is a chronic, painful immune-mediated inflammatory skin disease and has a lifelong remitting and relapsing course with varying factors that trigger exacerbations in susceptible individuals, thus making treatment challenging. Psoriasis is also associated with serious comorbidities and significant psychosocial disability with negative impacts on quality of life. The uncontrolled inflammation of psoriasis may contribute to commonly associated comorbidities, including cardiovascular (CV) disease (including hypertension and increased risk for myocardial infarction, stroke, and CV death), obesity, type 2 diabetes, arthritis, and chronic renal disease. Psoriasis is also associated with serious psychiatric comorbidities, including depression, anxiety, and suicidality, as well as substance abuse.

The current therapeutic options for moderate to severe plaque psoriasis include phototherapy, topical agents (e.g., corticosteroids), conventional systemic therapy (e.g., cyclosporine, methotrexate, and oral retinoids), and biologic therapy including TNF-α antagonists (adalimumab, etanercept, infliximab), anti-IL12/IL23 and anti-IL17 (ustekinumab, secukinumab, ixekizumab). The conventional therapies are associated with dose- and treatment-limiting options. The most common reasons for discontinuation of these therapies are lack of efficacy, adverse events (AEs), and treatment inconvenience. The biologic agents have been associated with higher objective response rates in clinical trials. However, even with these newer agents, most patients do not achieve optimal efficacy, such as total skin clearance. Although newer treatment options provide improved outcomes compared with traditional systemic therapies, there remains a significant unmet patient need for novel agents and mechanisms that can provide a rapid onset of effect, improved and sustained skin clearance, and minimization of drug-specific safety concerns (e.g. serious infections including opportunistic infections and tuberculosis, malignancies including lymphoma, immunogenicity and demyelinating neurologic events).

2.1.4. Management

The primary goal of psoriasis therapies is clearance of psoriatic plaques. Milder forms of psoriasis are typically managed with topical therapies, while more extensive or severe forms of psoriasis are typically managed with phototherapy or systemic therapy, which includes small molecules, usually given orally, and biologics, which are large molecules usually given by injection or infusion.

In clinical practice, tumor necrosis factor (TNF) antagonists were the first biological therapies approved for psoriasis and represent a current treatment option for moderate-to-severe chronic plaque psoriasis.

Ustekinumab (human IgG1 /κ monoclonal antibody against the p40 subunit of both IL-12 and IL-23 cytokines), secukinumab (human IgG1 monoclonal antibody against IL-17A), and ixekizumab (human IgG4 monoclonal antibodies against IL-17A cytokine) have also been approved in Europe, the United States and Canada for the treatment of patients with moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. There is a small proportion of subjects receiving biologic therapy due to a variety of reasons including lack of effectiveness, inability to secure insurance coverage or payment for the recommended biologic therapies, safety concerns, lack of understanding of therapy use or monitoring, etc. Many subjects do not achieve adequate response, as defined by subjects achieving at least a 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75), with anti-TNF agents and find that current therapies lose efficacy over time. A reduction in long-term efficacy has been described with other biologic treatments more notably at lower doses or with intermittent treatment and compliance in psoriasis patients is found generally to be poor.

2.2. About the product

Tildrakizumab is a recombinant monoclonal antibody which specifically binds to the p19 subunit of human IL23, thereby inhibiting IL23 signalling.

Type of Application and aspects on development

- Legal basis

The applicant Almirall, S.A. submitted on 6 March 2017 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tildrakizumab 100 mg solution for injection in a prefilled syringe. This application concerns a centralised procedure (according to Regulation (EC) No 726/2004), mandatory scope (Article 3(1)), Annex (1) Biotech medicinal product. The application been submitted in accordance with Article 8.3 in Directive 2001/83/EC (i.e. dossier with administrative, quality, non-clinical and clinical data), as new active substance.

- Accelerated procedure

N/A

- Conditional approval

N/A

- Exceptional circumstances

N/A

- Biosimilar application

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

On 06 March 2014, Merck Sharp & Dohme (Europe), Inc received an agreement on the Paediatric investigation plan granting a deferral and a waiver for tildrakizumab (Anti-human interleukin 23 p19 humanised IgG1/Ig kappa mAb, MK-3222) (EMEA-001451-PIP01-13), solution for injection, subcutaneous use, for the treatment of psoriasis (EMA/112332/2014).

- Scientific Advice applications

The company submitted scientific advice applications as mentioned below.

21-07-2011: EMEA/H/SA/2165/1/2011/III (quality and preclinical development)

24-05-2012: EMEA/H/SA/2165/1/FU/2012/III (quality, preclinical, and clinical development)

2.2.1. Introduction

The finished product is presented as solution for injection containing 100 mg of tildrakizumab as active substance. Tildrakizumab is human monoclonal IgG1 antibody targeted against the p19 subunit of the human interleukin-23 (IL-23). The mode of action is the down-regulation of IL-23 signalling, thereby dampening the expression of inflammatory cytokines which are elevated in many autoimmune diseases.

Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

The product is available in single-use pre-filled syringe for subcutaneous administration. Each pre-filled syringe is equipped with a passive needle guard and needle cover. Each pack-size contains 1 or 2 pre-filled syringes.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied in the development of the control strategy.

2.2.2. Active Substance

General information

Tildrakizumab is a monoclonal antibody that binds to human IL-23. It is composed of two identical heavy chains (HC) of 446 amino acids each and two identical light chains of 214 amino acids each linked by interchain disulfide bonds. The monoclonal antibody tildrakizumab is of the IgG1 subclass and contains kappa light chains. Tildrakizumab contains 16 disulfide bonds, which are consistent with the pattern known for the IgG1 subclass. The molecule is glycosylated on asparagine 296 (Asn296) on the heavy chain. Typically, the C-terminal lysines of both heavy chains are clipped and a small degree of proline α-amidation is also detected on the C-terminus. The N-terminal glutamines on the heavy chains are converted to pyroglutamate for the majority of the product.

The molecular characteristics were determined by mass spectrometry, peptide mapping, and N-glycan profiling. The antibody is heterogeneously glycosylated at Asn296 within the Fc domain of each heavy chain. The dominant glycoform is the fucosylated agalacto biantennary glycan form (G0F). The observed molecular weight of the most abundant form of the intact antibody is 147.0 kDa, while the most abundant forms of the heavy and light chains are 50.0 kDa and 23.5 kDa, respectively. These masses are consistent with the expected values based on the translated amino acid sequence and the typical N- and C-terminal modifications.

The secondary structure of tildrakizumab contains β-sheet domain as indicated by (FTIR). The tertiary structure of tildrakizumab is well defined by Near-Ultraviolet Circular Dichroism and Intrinsic Fluorescence. Based on the value of the peak maxima from intrinsic fluorescence, it can be deduced that, on average, the tryptophan residues are exposed to the environment within the tildrakizumab protein structure.

Manufacture, characterisation and process controls

Tildrakizumab active substance is manufactured according to Good Manufacturing Practices. Release testing is performed at a number of different manufacturing sites

Description of manufacturing process and process controls

The tildrakizumab active substance manufacturing process has been adequately described and reflects a standard process for monoclonal antibodies. Main steps are fermentation, recovery and purification. The upstream cell culture process consists of three consecutive stages (inoculum expansion, seed bioreactor expansion, and cell culture and antibody production in a production bioreactor. The upstream process ends with a bioreactor harvest and initial recovery step. The antibody is subsequently purified and polished using standard chromatography techniques, virus inactivation, viral filtration, and ultra-/diafiltration. The filtered active substance is stored in bags at the recommended storage condition based on the provided stability data. Reprocessing is not part of the tildrakizumab active substance manufacturing process. The ranges of critical process parameters (CPPs) and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. An adequate batch numbering system is in place. The active substance manufacturing process is considered acceptable.

Tildrakizumab active substance is filled into sterile bags. The fluid contact layer complies with Ph. Eur. 3.1.7. None of the studied extractables or leachables pose a toxicological concern at the levels identified.

Control of materials

The applicant described the construction of the expression plasmids, the transfection of the expression cell line and the selection of the production clone in detail. The tildrakizumab antibody was developed following immunizing mice with IL-23.

CHO (DXB11)-cells are used as host cell line for the expression of the tildrakizumab antibody. A two tiered cell banking system is used. A master seed bank (MSB), master cell bank (MCB) and two working cell banks (WCB) were established. The second WCB has been produced without foetal bovine serum. An end-of-production cell line was established and genetic stability and viral safety investigated.

Cell bank testing and characterisation was performed according to the requirements defined in ICH Q5A and Q5D. The data of cell bank characterisation demonstrate the absence of microbial and viral contaminants, as well as endogenously encoded retrovirus-like particles, except A type and a low level of C type retrovirus particles. No reverse transcriptase activity was measured.

The stability of the WCB during storage is monitored continuously Stability of the MCB during storage is tested every two years after manufacturing. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

The restriction patterns and hybridization patterns of the EPC were identical to that of the MCB. Furthermore, the mean target gene copy numbers per cell are comparable.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. Porcine trypsin has been used during early development and foetal

bovine serum (FBS) also during freeze down of the MCB and the first WCB. Sufficient information regarding the risk of Transmitting Animal Spongiform Encephalopathy and porcine virus contamination has been provided.

Control of critical steps and intermediates

The critical steps and in-process control limits for the tildrakizumab active substance upstream and downstream manufacturing process have been provided. The critical steps have been identified and CPPs and key operating parameters (KOPs) were defined based on impact on quality attributes or process consistency, respectively. Appropriate in-process controls are in place to assure microbial control. Non-KOPs are operating parameters whose variability does not impact a key process attribute (KPA) or critical quality attribute (CQA), but is still controlled to a defined range. The assigned proven acceptable ranges (PARs) for the CPPs and KOPs are based on the results obtained by the process performance qualification and process validation studies. Action taken if limits are exceeded is specified.

Initial normal operating ranges (NORs) have been defined for Phase 3 clinical batches manufacturing and were reviewed based on process characterization studies. The ranges of several process parameters were narrowed to be in the range of the proven acceptable ranges of the commercial manufacturing process. The NOR is defined as “The range of an operating parameter that is used for routine manufacture, accounting for the control limits of the equipment and its associated known variability.”

Intermediates specifications, storage conditions and shelf life were sufficiently described and justified.

The analytical methods used for in-process testing have been described and the method verification/validation results briefly presented.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The validation of the tildrakizumab active substance manufacturing process was conducted taking the principles of the CHMP “Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in regulatory submission” into account. The critical quality attributes (CQA), key process attribute (KPA), key operating parameter (KOP) and non-KOP have been defined during the process characterisation studies (PCS). The normal operating ranges (NORs) and /or proven acceptable ranges (PARs) assigned during the PCS (design-of-experiment (DOE) and/or one-factor-at-a-time (OFAT) analyses) have been used as acceptance criteria during the process validation studies.

The tildrakizumab active substance manufacturing process has been validated adequately. Consistency in production has been shown on three subsequent full-scale commercial batches manufactured using the commercial process. All acceptance criteria for the critical process parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces tildrakizumab active substance of reproducible quality that complies with the predetermined specifications and in-process acceptance criteria. Furthermore, testing for adventitious agents and bioburden provided suitable assurance with respect to microbial contamination.

Intermediate hold time studies have been performed for the active substance manufacturing process steps. Biochemical as well as microbial parameters have been evaluated. A suitable number of batches were tested. The validated hold time was assigned.

Resin lifetime studies have been performed for all chromatography steps in the active substance manufacturing process. Adequate small scale studies have been performed which cover the maximal intended resin lifetime. The results support the assigned lifetimes. Concurrent validation at manufacturing scale is ongoing. During the validation studies some minor deviations have been found which have been sufficiently justified.

UF/DF membrane re-use is suitably described.

Shipping validation has been performed using active substance container bags filled with water for injection (WFI). The container closure integrity was tested and the system found to be suitable for the tildrakizumab active substance shipment.

Extractable and leachable studies have been performed on the process contact materials used during the manufacturing of the tildrakizumab. The studies did not detect leachables or extractables which are considered to pose high risks. The identified extractables and leachables are considered well below the daily maximal permissive expose (PDE) according to ICH Q3C.

Manufacturing process development

The manufacturing development including the control strategy defined for tildrakizumab has been designed taking the principles of ICH Q8-11 into consideration. The tildrakizumab active substance CPPs and CQAs have been defined according to ICH Q8. The commercial active substance manufacturing process was developed in parallel with the clinical development program. Process I active substance was used for non-clinical studies. Process I was up-scaled and transferred to another site. This produced material was used for Phase 1 and 2 clinical trials. Process I underwent further refinement resulting in process II. The main changes were usage of a WCB instead of a MCB, column changes and a change in the active substance formulation among other smaller changes. The material of process II was used for phase 3 clinical trials. Finally, process II was transferred to the commercial site and up-scaled. The main change beside facility and scale fits was the introduction of a new WCB, which was cultured and is stored without using FBS.

The results demonstrate, with the exception of minor differences, high comparability between the active substance and finished product batches produced during tildrakizumab development up to the commercial process. For further understanding of the process and to determine critical parameters and attributes the applicant performed process characterisation studies. Prior to the Process Characterisation studies a risk assessment was performed using FMEA principles.

KPAs, KOPs and non-KOPs have been assigned considering the outcome of the Process Characterisation studies or claims from the viral clearance studies.

Characterisation

The tildrakizumab active substance has been extensively characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. The analytical results are consistent with the proposed structure. Biological characterisation of tildrakizumab indicates that this antibody has the ability to bind the p19 subunit of the human IL-23 and to specifically bind to Fcγ receptors, C1q and FcRn as expected of an IgG1.

Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The product-related impurities are standard for a monoclonal antibody and include aggregates, fragments, charge variants, oxidised variants and deamidated variants. The product-related impurities are suitably controlled. Process-related impurities included host cell proteins, host cell DNA and protein A which are all controlled through the active substance release specifications.

Specification

The active substance specification includes tests for description, identification, potency, purity, impurities, physico-chemical tests and microbiological tests.

The panel of tests is considered sufficient to allow for routine control of the quality of this monoclonal antibody. The specifications were established using a tolerance interval approach based on release and stability data. The approach is acceptable and the assigned acceptance criteria are considered adequate.

Analytical methods

The active substance specification allows adequate control of identity, purity and potency. The analytical procedures have been described. The potency of tildrakizumab active substance samples is determined, relative to the reference standard, using a functional cell-based assay.

Validation

Validation was performed on tildrakizumab active substance samples. For the manufacture of tildrakizumab finished product, active substance is delivered as formulated bulk solution containing the exact formulation of the final product, and no excipients are added during the finished product manufacturing process. Therefore, active substance is considered sufficient for validation of both active substance and final product. The material used is representative of commercial active substance and final product.

Compendial analytical procedures have been verified per ICH Q2 (R1). For the Endotoxin test a Low Endotoxin Recovery (LER) study was performed to demonstrate that tildrakizumab active substance does not exhibit masking effects over a period of 7 days. Bioburden recovery is not negatively impacted by tildrakizumab active substance or formulation buffer.

Non-compendial analytical procedures have been validated according to ICH Q2 (R1).

Batch analysis

Representative batch analysis data are provided for tildrakizumab lots manufactured for the purpose of non-clinical and clinical testing, development as well as process validation of the active substance manufacturing process. Batch analysis data for an appropriate number of process performance qualification (PPQ) lots manufactured were presented.

In summary, data for a number of active substance batches has been provided which includes process performance qualification (PPQ) lots and clinical lots manufactured at the commercial scale and site. All batch data were within specifications and demonstrate that the process is capable of producing an active substance of consistent quality.

Reference materials

Three primary reference standards (PRS) and one secondary reference standard (SRS) have been used throughout development. All reference standards were tested using the registered active substance release tests as well as extended characterisation testing. The acceptance criteria were tighter for some assays, in particular the potency assay. Reference standards are requalified every two years. The testing scheme for ongoing reference standard qualification is described in the dossier. A protocol for the generation of future reference standards is provided which includes details of the equivalency testing approach to ensure comparable potency.

Stability

Real-time stability data from formal stability studies (FSS) at the recommended storage condition are available up to 36 months for four tildrakizumab active substance lots manufactured. The lots evaluated in FSS, as well as the PPQ stability lots, are fully representative of the commercial material made in the commercial plant at commercial scale.

The presented stability studies support the proposed storage period of 36 months. All results are within specifications.

Data from accelerated, stressed and freeze-thaw stability studies have been provided. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The tildrakizumab finished product is presented as a sterile, preservative-free solution in a single-use, prefilled syringe (100 mg tildrakizumab/syringe) which is assembled into a safety device (finger flange, rigid needle shield, needle guard) referred to as a combination product. The prefilled syringe is made of Type I glass, Stainless steel Needle; Polypropylene Rigid Needle Shield; Fluropolymer lamination, latex-free plunger stopper.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The drug product is filled with an excess volume to ensure a deliverable volume (1 ml). The excipients were selected on the basis of appropriate formulation development studies. Formulation composition and dosage form were developed as part of an extensive evaluation of factors such as buffer type, stabiliser/tonicifier and surfactant concentration. The robustness and stability of the commercial formulation has been adequately justified.

The tildrakizumab finished product is developed as a pre-filled syringe (PFS) combined with a safety device (combination product). During the development, a design verification study as well as a design validation was conducted. The studies have been performed according to applicable regulations. In the regional information a Declaration of Conformity by the legal manufacturer- is provided.

Stability studies under normal, accelerated and stressed conditions have been performed for the PFS and the combination product. No impact on technical attributes (extractable volume, gliding force, etc.) has been detected.

The suitability of the container closure system of the tildrakizumab has been adequately assessed. Compendial testing as well as ISO standards were used to show suitability. Stability including photostability and container closure integrity testing were performed. Extractables and leachables detected are commonly seen in PFS systems and do not raise concerns regarding patient safety

The microbiological attributes are adequately described as sterile and preservative-free. Aseptic processing is verified by media fills which are regularly performed. Container Closure integrity, release and stability testing add additional assurance. A rabbit pyrogen test has been performed which showed no pyrogenic response. The compatibility of the tildrakizumab is verified by development of the container closure system and finished product stability studies.

Manufacture of the product and process controls

The manufacturing process of the tildrakizumab finished product consists of two stages: 1) manufacturing of the PFS; 2) assembly of the safety device to the PFS (combination product). The manufacturing of the PFS is performed as standard fill-and-finish process, with no addition of new excipients. Both processes are briefly described and the process controls have been indicated. Reprocessing has not been reported in the dossier and is therefore not assumed to be applied for.

The proposed target acceptance criteria are listed for both critical and in-process microbial parameters.

The manufacturing process validation is acceptable and the process is demonstrated to be capable of producing batches of consistent quality.

The tildrakizumab finished product manufacturing process performance qualification was conducted using three consecutive lots. The acceptance criteria were aligned with the finished product release specifications. The results met all pre-defined acceptance criteria.

Taken together the manufacturing process qualification demonstrated that the process is robust and consistent.

The microbial retention study demonstrated that under worst case conditions the filtration process is capable of producing aseptic finished product. Filter integrity testing is performed pre- and post-filtration using the bubble point method. The applicant performed a filter compatibility study to show that the filter material used does not affect the quality of tildrakizumab. Aseptic filling is verified using media fills. All environmental monitoring results show no action limit excursions.

The materials used during tildrakizumab manufacturing process have been tested for compatibility. A risk ranking was performed and materials identified as medium and high risk were subjected to leachable testing with finished product solution. Data concerning the extractable and leachables evaluation have been provided.

Shipping of the tildrakizumab is performed using an active and passive thermal protection system (TPS). The shipping procedure is considered validated.

Product specification

The finished product specification includes tests for appearance and description, identification, assay, purity, impurities, potency, pharmaceutical technical tests and microbiological tests. The combination product specification includes test for appearance, device functionality and extractable volume.

In general the finished product specifications are acceptable and take account of the requirements of the Ph. Eur. monographs for Parenteral preparations and Monoclonal antibodies for human use (01/2012:2031), respectively. The specifications have been developed in accordance with ICH Q6B. A specification is also applied to control the functionality of the device component. In the absence of a proposed control on silicone levels at release and stability of the finished product the applicant has confirmed that the supplier of the syringe barrel will control the level of siliconisation of the container at toxicologically justified levels to ensure sub-visible particles remain compliant with specifications over the lifecycle of the product. The tildrakizumab finished product acceptance criteria were established using a tolerance interval approach based on release and stability data. The dataset used to set release specifications comprised data of several batches. For stability specifications, several finished product lots (clinical, pre-filled syringe) were statistically analysed.

The analytical procedures for tildrakizumab finished product are sufficiently described.

Some analytical procedures used to test both tildrakizumab active substance and finished product are discussed in the respective active substance section.

Validation summaries for analytical procedures used to test tildrakizumab active substance and finished product are provided in the respective active substance section. Analytical procedures were validated in accordance with the ICH Q2(R1). Compendial methods were appropriately verified for their intended use. Methods for determination of syringe functionality have been evaluated in accordance with the principles of ISO-7886-1.

Analytical methods

For the manufacture of the finished product, tildrakizumab active substance is delivered as formulated bulk solution containing the same formulation as the final finished product, and no excipients are added during the finished product manufacturing process. Therefore many of the analytical methods are identical for finish product and active substance.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Representative batch analysis data are provided for tildrakizumab finished product lots manufactured for the purpose of non-clinical and clinical testing, development as well as process validation of the manufacturing process.

For all batches, predefined acceptance criteria which were in effect at time of batch analysis and release were met.

Impurities

Process-related impurities include particles that may arise from the manufacturing process. All prefilled syringes are 100% inspected for visible particles at the time of manufacture. During release and stability testing, the appearance of the tildrakizumab finished product is tested according to Ph. Eur. 2.9.20. Any observed particles are further characterised.

Product-related substances and impurities are monitored in tildrakizumab finished product at release and on stability. There are no new product-related impurities observed in the finished product relative to the active substance on stability.

A quality risk management approach per ICH Q3D was conducted to assess potential sources for the introduction of elemental impurities within the tildrakizumab prefilled syringe (Option 2b). The following sources were considered: product contact materials during active substance manufacturing, excipients and water, product contact materials during finished product manufacturing, primary packaging components and silicone oil.

Reference materials

Because the compositions of tildrakizumab active substance and finished product are the same (no excipients are added during the finished product manufacturing process), the use of these primary and secondary reference standards obtained from active substance batches for testing both tildrakizumab active substance and finished product is appropriate.

Stability of the product

Stability has been demonstrated for the proposed shelf life based upon real time stability data of tildrakizumab PFS lots manufactured at both the clinical and commercial sites.

The available stability data for samples stored at the recommended storage conditions show good stability with no significant trends observed. The parameters tested are the same as for release. The stability indicating parameters are acceptable and the stability monitoring program conforms to ICH Q5C.

Data from accelerated, stressed and cold stress, leachables and photostability studies have been provided.

In use stability data supported the following claim: "Unopened PFS of Ilumetri may be removed from the refrigeration and stored up to 25°C for a single period of up to 30 days. Once removed from the refrigerator and stored under these conditions, discard after 30 days or by the expiry date printed on the container, whichever occurs first. A field for the date is provided on the carton to record the removal and discard date". Based on available stability data, the 36 month shelf-life when stored at 5ºC ± 3ºC as stated in the SmPC is acceptable.

Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. no materials of animal or human origin are used during production (fermentation or purification). Valid EDQM certificates of suitability have been provided for the animal-derived materials used during selection of the tildrakizumab expressing clone and establishment of the cell banking system.

Virus safety

Other than the cells themselves, no material of animal origin is added during fermentation. The cell banking system has been extensively screened for adventitious viruses using a variety of in vitro and in vivo assays. The tests failed to demonstrate the presence of any virus contaminants in the cell banks with the exception of intracellular type A and extracellular type C retrovirus-like particles which are well known to be present in rodent cells; this is acceptable however, since there is sufficient capacity within the tildrakizumab manufacturing process to inactivate/remove such virus particles.

Effective reduction of enveloped viruses was demonstrated for the low pH inactivation step. Further reduction was observed for the entire panel of viruses for the various chromatography steps. Effective reduction was demonstrated for all four viruses for the retentive virus filtration step. At the end of the tildrakizumab fermentation procedure, general testing for adventitious viruses is performed as well a specific tests to detect minute virus of mice.

In summary, the TSE and virus safety of tildrakizumab has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied elements of an enhanced approach in the development of the active substance and their manufacturing process.

The tildrakizumab manufacturing process uses state-of-the-art methodologies frequently used for the manufacture of monoclonal antibodies. The process is well-described, characterised and validated. The control strategy for the active substance is well elaborated giving the applicant a significant amount of

process knowledge. The overall control strategy can be deemed sufficient to support the manufacture of active substance of consistent quality. Specifications for the active substance have been appropriately justified and acceptable acceptance criteria assigned. The active substance is stable at the intended storage condition and stability has been supported by data.

Formulation studies for the finished product are described and are considered acceptable. The discussion of manufacturing process development is described in sufficient detail, and the development of the control strategy is well explained and justified. In general, the process validation studies show the manufacturing process to be sufficiently validated. The analytical methods are adequately described and validated. Specifications for the finished product have been appropriately justified and acceptable acceptance criteria assigned. The primary container closure system is a PFS which is assembled into a Passive Needle Guard Assembly as safety device (combination product). The details of this device and its control are acceptable. The proposed shelf-life of the finished product is acceptable based on the stability of pre-commercial scale batches. The comparability of these batches to the commercial-scale batches has been shown in the comparability exercises.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant submitted a comprehensive non clinical scientific package to support the application for the treatment of psoriasis in adult patients.

2.3.2. Pharmacology

Tildrakizumab is a humanised recombinant IgG1 that binds to the p19 subunit of IL-23, thereby blocking its interaction with the IL-23 receptor. IL-23 is a pro-inflammatory cytokine that has been implicated in the pathogenesis of a number of chronic inflammatory diseases including psoriasis. The potential of tildrakizumab to be effective in the treatment of psoriasis has been investigated in non-clinical studies using *in vitro*, *ex vivo* and *in vivo* techniques.

In vitro

Comparison of the amino acid sequences of IL-23p19 between human and various preclinical species revealed that cynomolgus monkeys had a 98% homology to humans. The level of homology dropped off significantly with sequences which were not from non-human primates and only 77% and 72% homology was seen between human and rat and mouse respectively. In line with these findings Biacore surface plasmon resonance measurements revealed a K_D of tildrakizumab for human IL-23p19 of 297 pM and 47 pM for cynomolgus monkeys. No detectable binding to murine IL23-p19 was observed.

Biological activity of tildrakizumab was determined using three different cell-based *in vitro* assays. IL-23 dependent proliferation, STAT3 phosphorylation or IL-23-stimulated release of IFN-γ was inhibited by tildrakizumab with comparable IC_{50} values ranging from 59 to 187 pM. IC_{50} values for inhibition of IL-23 dependent STAT3 phosphorylation were comparable between human IL-23 or cynomolgus monkey IL-23, indicating functional similarity between the two species. Taken together this data supports that tildrakizumab will have relevant pharmacological activity in cynomolgus monkeys but not in mice or rats.

Due to the lack of cross-reactivity with mouse IL-23p19 and in order to test the potency efficacy in vivo a surrogate antibody, SCH 900598, was generated against the mouse IL-23p19. This antibody, however, had a significantly lower affinity when compared to tildrakizumab with a K_D of 3.5-6.7 nM. Functional assays similarly demonstrated a much higher IC_{50} of between 8-11 nM, again suggesting much lower potency for inhibiting IL-23p19 dependent signalling. Due to the lower potency of the mouse surrogate, the dose was scaled up for maximal efficacy in an *in vivo* colitis model.

The anatomical distribution of *IL-23p19*, its 2 receptor subunits (*IL-23R* and *IL-12Rβ1*), and *IL-12/23p40* were assessed by quantitative gene expression in human tissues and compared to the anatomical profiles of the corresponding genes in cynomolgus monkey tissues and tissues from mice. Although the gene expression levels are highly variable between the species, the overall gene expression pattern is similar, being most expressed in tissue belonging to the immune system and gastrointestinal compartment. Enhanced expression of p19 and p40 mRNA was found in human diseased tissue from either psoriasis patients or Crohn´s Disease patients compared to normal tissue.

In vivo

The mouse surrogate antibody, SCH-900598, was used in a number of in vivo models in which increased IL-23 is linked to the pathology of the disease. Two different models of colitis, a T-cell dependent and an anti-CD40 model, were used and where efficacy of SCH-900598 was assessed. In both models SCH-900598 was effective although relatively high levels of up to 30 mg/kg were required. Although the disease indication differs than that in the current MAA these studies could be considered to be supportive in suggesting that the inhibition of IL-23 in inflammatory diseases can have significant effects on the pathology seen.

For the proposed indication of psoriasis the most relevant in vivo efficacy data has been provided in a humanised mouse model of psoriasis. Here immunosuppressed mice were transplanted with clinically symptomless skin grafts from psoriasis patients. The data has been provided in the form of a peer reviewed publication and not as a study report. As such the materials and methods section is quite succinct and makes references to other literature sources for the description of the xenotransplantation experiments and the samples. In this model an anti-human IL-23p19 mAb blocked the development of psoriasis as assessed by microscopy measuring acanthosis and papillomatosis at 5 weeks post implantation compared to an isotype control antibody. The efficacy was comparable to that of an anti-TNFα mAb which was used for comparison. Of note, the dose used in the study is quite high at 60 mg/kg considering the proposed clinical dose of 200 mg. Although the antibody used in the study was not tildrakizumab, but an unrelated mouse monoclonal targeting IL-23p19, the study can be seen as supporting the potential of tildrakizumab in the treatment of psoriasis.

Secondary pharmacodynamics

As tildrakizumab is an IgG1 antibody, it has the potential to induce ADCC and/or CDC. However, this was not addressed by the applicant. Tildrakizumab binds to a soluble target and inhibits IL-23-induced signalling (e. g. phosphorylation of STAT3). As tildrakizumab binds to IL-23p19 the interaction of p19 with subunit IL-23R is impaired. In theory, a binding of tildrakizumab to IL-12Rβ1 via IL-23 is

conceivable. The applicant has provided a thorough discussion that this scenario would not occur in the clinical setting.

The role of IL-23 blockade was assessed in three models of infection with intracellular pathogens. Mice were challenged with either *Mycobacterium bovis* BCG, *Salmonella* or *Listeria monocytogenes* and treated with the mouse surrogate antibody or respective controls. In summary, neutralizing IL-23 was less immuno-suppressive than neutralizing both IL-23 and IL-12. However, IL-23 and its involvement to the Th17 axis are also important for the host's defence against extracellular pathogens, especially in mucosal immunity. In summary, the data suggest that IL-23-specific blockade would not be expected to incur any worse infection risk profile in humans than the existing anti-IL-12/23p40 therapy. However, impairment in host defence towards special pathogens cannot be fully excluded with the non-clinical data. Therefore, clinical monitoring of serious infections is addressed in the SmPC and in the RMP.

Safety Pharmacology

In line with ICH S6 (R1) no stand-alone safety pharmacology studies have been performed with tildrakizumab and instead appropriate endpoints were incorporated into the repeat dose toxicities studies in in monkeys. No tildrakizumab-related effects on the cardiovascular, respiratory and central nervous systems were noted.

Overall, the provided non-clinical pharmacology package is considered sufficient to support the marketing authorisation application in psoriasis patients.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics of tildrakizumab were evaluated in mice, in which tildrakizumab is not cross-reactive, and in cynomolgus monkeys, where tildrakizumab does cross-react.

Methods of analysis

Immunoassays used to analyse tildrakizumab, anti-tildrakizumab antibodies and IL-23 expression based on the Meso Scale Discovery platform were developed and validated appropriately to be used for the GLP toxicity studies. The assays mostly displayed appropriate levels of specificity and sensitivity. It is noted that the limit of quantification for ADAs is quite high at 0.781 μg/ml.

Absorption:

Single-dose administrations after IV and SC injection were performed in mice and cynomolgus monkeys. Due to a lack of cross-reactivity in mice any of the parameters measured do not reflect any effects of on-target binding. Linear increases in systemic exposure levels were seen in cynomolgus monkeys in response to increasing doses. Bioavailability following single dose SC administration varied from 40% to 91%. With a T_{max} at 3-4 days following SC administration tildrakizumab appears to be slowly released when administered by this method. The mean half-life of tildrakizumab was 18.9 days across all doses investigated. However, the pharmacokinetic parameters measured are limited by the fact that several of the animals developed neutralising ADAs, particularly in the highest dose, and these animals were subsequently removed from the pharmacokinetics analysis.

Pharmacokinetic parameters following repeat dosing were measured as part of the repeat dose toxicity studies in cynomolgus monkeys. The bioavailability measured was high at 86% after SC administration with systemic exposures displaying increases with doses and independent of sex. Some evidence of accumulation of doses was seen with C_{max} and $AUC_{(0\text{-}14\ d)}$ levels higher when measured after the 7th dose than those after the 1st dose. In the measured toxicokinetics samples the number of animals positive for ADAs was low and in most cases they did not appear to be neutralising.

Changes in formulation did not alter the pharmacokinetic parameters when a comparability study in both mice and monkeys was done following a change in formulation from solution to a lyophilised form.

Distribution

In a tissue distribution study in mice, fluorescently labelled tildrakizumab showed the expected non-specific organ distribution typical of endogenous IgG.

Metabolism

As is appropriate for a monoclonal antibody no studies regarding the metabolism of tildrakizuamb were performed. As a protein, tildrakizumab is expected to be degraded into small peptides and constituent amino acids.

Excretion

In line with ICH S6 (R1) guidance, no dedicated mass balance excretion studies have been performed with tildrakizumab. Low levels of tildrakizumab up to 0.252 µg/ml were evident in breast milk at PPD28 in which dams were dosed up to parturition. This decreased significantly over time at PPD91, in line with the likely clearance of the drug from the dams.

Drug-drug interaction studies

Non-clinical PK drug interaction studies were not conducted. This is acceptable, since tildrakizumab as a monoclonal antibody is not metabolized via CYP450 enzymes. However, a potential impact of tildrakizumab on the PK of other drugs was evaluated in vitro in cultures of human hepatocytes. The study showed that expression of IL-23 receptor is negligible in human hepatocytes and IL-23 does not affect expression of CYP1A2 and CYP 3A4. Thus, tildrakizumab is not expected to affect the PK of other drugs.

2.3.1. Toxicology

Toxicology studies with tildrakizumab were conducted in cynomolgus monkeys which were shown to be a relevant species, based on the binding of tildrakizumab to cynomolgus IL-23p19. Overall, the toxicology programme is in accordance with ICH S6(R1).

Single dose toxicity

No formal single dose toxicity studies have been performed. Clinical observations were made as part of a PK study in cynomolgus monkeys where doses up to 40 mg/kg were tolerated without clinical effects. Furthermore, the potential for off-target toxicities was assessed in mice where no pharmacological activity is expected. Doses of up to 200 mg/kg were tolerated without overt toxicity seen.

Repeat dose toxicity

Toxicity of tildrakizumab was evaluated in repeated dose studies of 3-months and 9 months treatment duration. The two studies did not reveal tildrakizumab-related noteworthy findings, except for inflammatory infiltrates at the SC injection sites.

It is noted that in both studies, histopathology data for the low- and mid-dose animals from the end of dosing sacrifice are lacking. This is not in accordance with the Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*), which recommends that for non-rodents, histopathology should be provided on all organs and tissues that are evaluated macroscopically since the number of evaluated animals is small. Nevertheless, the lack of the histopathology data for the low and mid-dose animals may be accepted, since the data from the high-dose animals at the end of treatment did not identify target organs of toxicity, except for the SC injection sites. Histopathology data from recovery animals

from the 9 months study were generally unremarkable. The toxicity studies did not reveal tildrakizumab-related effects in any of the parameters evaluated.

Systemic exposure in both studies was independent of sex, increased in a dose proportional manner and demonstrated accumulation with repeat dose administration. The accumulation is most likely related to the delayed clearance of the antibody which displayed a half-life of between 17.7-21 days which is consistent with an antibody of the IgG1 class. Of note, no ADAs were detected in any of the animals in the 9-month toxicity study, whilst only 1 animal in the 3-month study tested positive for ADAs which appeared to be neutralising based on the reduced exposure in this animal. It is noted that the limit of quantification for ADAs is quite high at 0.781 μg/ml. It is accepted that despite the limitation with the developed assay for ADAs sufficient exposure levels appear to have been reached in the long-term repeat dose toxicity studies.

In summary, no adverse effects were observed in the tildrakizumab repeated dose studies. In both studies, the NOAEL was the highest dose administered. In the 3-months study, the NOAEL was 140 mg/kg following either IV or SC administration every 2 weeks; in the 9-months study, the NOAEL was 100 mg/kg SC Q2W. Thereby exposure in cynomolgus at the NOAEL was > 100 – 200-times higher than the human exposure at the recommended SC dose of 200 mg, administered once every 12 weeks. The exposure achieved in cynomolgus monkeys at the NOAEL provides a large margin to the exposure at the proposed clinical dose.

Genotoxicity

As a monoclonal antibody, tildrakizumab would not be expected to interact with nucleic acids. No genotoxicity studies were performed, in line with ICH S6(R1).

Carcinogenicity

Classical carcinogenicity animal studies were not conducted; instead the risk of carcinogenicity was assessed based on a weight of evidence approach. To this end, the applicant has conducted several *in vivo* studies in mouse tumour models and an extensive analysis of current literature.
Literature evidence suggests that IL-23 p19 is increased during tumourigenesis, where it decreases immune surveillance by CD8 T cells. Although evidence from knock-out mice suggests that loss of both IL-23 and IL12 together is associated with increased cancer risk, the inhibition of IL-23 signalling alone is likely to result in a decreased risk. Mechanistic studies performed by the applicant have shown that tildrakizumab did not alter the growth of tumours in a xenograft model. Histopathological analysis of tissues from the 3 and 9 month repeat dose toxicity studies did not indicate any evidence for pre-neoplastic changes. Taken together the weight of evidence supports the position that tildrakizumab is unlikely to be associated with increased carcinogenic risk. Nevertheless, malignancies will be monitored in the clinic during clinical studies and post marketing.

Reproductive and developmental toxicity

Reproductive and developmental toxicity of tildrakizumab was evaluated in cynomolgus monkeys.

Fertility was evaluated based on histopathological data from the repeated dose toxicity studies. While almost all females were sexually mature, the number of sexually mature males was limited. Nevertheless, considering the lack of findings in the repeated dose toxicity studies together with data of normal fertility of mice deficient in IL-23 or IL-23 R the data available from the repeated dose toxicity studies are considered sufficient. Tildrakizumab is not expected to have an effect on fertility.

Embryo-fetal developmental toxicity was assessed in a stand-alone study performed in cynomolgus monkeys treated by SC injection with 0, 10, 100 or 300 mg/kg every 14 days from GD 20 to 118. There were 2 abortions in the tildrakizumab groups with one each in the mid and high dose groups

which are comparable to the control group (total of 2) and lower than historical data from the facility. No tildrakizumab-related malformations or variations were observed in the live fetuses. Transfer of tildrakizumab to fetuses was evident with ratios of 0.6-0.8 foetal/dam observed. ADAs were present in several of the dams and also one fetus, however, except for the 1 dam and her fetus most instances of ADAs did not appear to be neutralising. The highest dose of 300 mg/kg was identified as the NOAEL and toxicokinetics analyses revealed a 227 margin of exposure to the proposed 200 mg dose.

A pre-postnatal development (PPND) study was performed in cynomolgus monkeys administered tildrakizumab by SC injection with 0, 10 or 100 mg/kg every 14 days from GD 50 to parturition with an associated TK study. TK analysis confirmed that off-spring was exposed to tildrakizumab. The fetal/maternal ratio for tildrakizumab serum concentration was approx. 1 on PND 7, 1.15 - 1.36 on PND 28 and 2.17 – 4.9 on PND 180. The increase in the infant/adult ratio is indicative of a slower clearance of tildrakizumab in infants compared to the maternal animals. Also, in this PPND study the incidence of fetal loss was comparable in tildrakizumab-treated groups (20% at 10 mg/kg; 7% at 100 mg/kg) and the control group (20 %) and was within the range of historical control data. In viable offspring, seven neonates died or were euthanized within 15 days of postnatal life: 1/12 (8%) in the control group, 2/12 (17%) in the 10 mg/kg group, and 2/14% (14%) in the 100 mg/kg group. Four of these deaths are attributable to maternal neglect, which is a common background finding in primigravid cynomolgus monkeys, or death of the mother and unsuccessful cross-fostering. However, two neonates in the 100 mg/kg group which died were found to be icteric and had pathological findings of lymphoid depletion and changes in the liver and kidney suggestive of a viral infection. Since these findings were considered of an unknown relationship to tildrakizumab the NOAEL for the study was considered the lower dose of 10 mg/kg. In the surviving infants, there were no tildrakizumab -related changes in any of the parameters evaluated.
Immunotoxicity endpoints were investigated in the surviving infants including measuring the levels of T-and B-lymphocytes as well as TDAR analysis. The results of these analyses did not reveal any tildrakizumab-related changes in lymphocyte numbers or TDAR responses. The systemic exposure levels at the time points at which the immunization was performed were much lower than would be seen during treatment. Nevertheless the applicant has made the argument that although the exposure level is low in the infants when measured at BD150 it is still more than 30 times the EC_{50} for IL-23. This argument appears logical and appropriate, thus accepted by the CHMP.
The TK analyses revealed that the findings at 100 mg/kg occurred an 85 fold margin of exposure to the 200 mg dose with a margin of exposure of 9 at the identified NOAEL. A risk assessment by the applicant for immune suppression and viral infection in relation to icteric neonatal deaths concluded that the there is no indication that immunosuppressive activity of tildrakizumab that would lead to an increased risk for bacterial or viral infections based on the results of the repeat toxicity studies, mechanistic studies where inhibition of IL-23p19 signalling did not affect host defence mechanism and the results of the immunotoxicity studies in infants in the PPND study.

In accordance with the agreed PIP, juvenile animal toxicity studies were not conducted to support a future use of tildrakizumab in paediatric patients.

Local tolerance

Tildrakizumab was locally well tolerated by rabbits when injected by the IV, intramuscular, intra-arterial and paravenous route. Local tolerance to tildrakizumab following SC administration, the proposed clinical route of administration, was evaluated as part of the repeated dose toxicity studies. Minimal perivascular mononuclear cell infiltrates were observed at the SC injection in all tildrakizumab-treated groups which was reversible.

Immunotoxicity

The immunotoxic potential of tildrakizumab was evaluated as part of the PPND study in infants from mothers treated with tildrakizumab throughout gestation. Based on these data, overt immunosuppression by tildrakizumab is not expected. Nevertheless, since IL-23 is required for generation of Th17 cells, an impaired IL-17-dependent immune response against pathogens cannot be excluded. “Serious infections” is therefore listed as “important potential risk” in the RMP.

Tissue cross-reactivity studies

The potential cross-reactivity of tildrakizumab with cryosections of normal human tissues and normal cynomolgus monkey tissues was assessed. In both studies, tildrakizumab staining was seen in cells and tissues which have not previously been associated with IL-23 expression. The Applicant has argued that since these staining were all cytoplasmic in nature it is unlikely that such tissue cross reactivity would be able to occur in vivo. As outlined in ICH S6 (R1), tissue binding per se does not indicate biological activity in vivo and cytoplasmic binding is generally not relevant. When taken in the context of the lack of adverse findings in the repeat dose toxicity studies of up to 9-months duration in cynomolgus monkeys, it is accepted that the observed tissue cross reactivity is of little relevance.

2.3.2. Ecotoxicity / environmental risk assessment

Tildrakizumab is a monoclonal antibody consisting of natural amino acids, and is therefore not expected to pose a risk to the environment. This is acceptable by CHMP.

2.3.3. Discussion on non-clinical aspects

The applicant has presented non-clinical in vitro data to demonstrate the pharmacological mode of action for tildrakizumab as an IL-23 inhibitor. Tildrakizumab binds to human IL-23p19 with a K_D of 297 pM and is cross-reactive with to cynomolgus monkey but not to IL-23p19 of murine origin. Thus, cynomolgus monkeys were selected as the relevant species for toxicology testing. The affinity of tildrakizumab is higher towards IL-23p19 of cynomolgus monkey origin (47 pM) compared to that of human origin.

Functional in vitro studies provide adequate information on the potency of tildrakizumab to inhibit IL-23-induced signal transduction and cellular responses.

In vivo studies in models of inflammatory bowel disease or psoriasis with IL-23p19 neutralising antibodies demonstrate pharmacologic activity and provide a proof-of-concept for the blockade of IL-23 in psoriasis.

The PK profile of tildrakizumab is considered as adequately characterised with single dose PK studies as well as TK measurements as part of the toxicity studies. No dedicated metabolic or excretion studies have been performed, however, this is in line with ICH S6 (R1) guidance.

The toxicity of tildrakizumab has been adequately characterised in cynomolgus monkeys which were deemed to be the only active species for relevant pharmacological activity. In the repeat dose toxicity studies tildrakizumab was very well tolerated and the main findings were inflammatory infiltrates at the injection site following SC administration of the mAb. The NOAELs identified providing margins of exposure >100 fold the proposed clinical dose. In a pre and post natal development toxicity study in monkeys, no related increase in pregnancy loss was observed at exposures up to 85 times the human exposure at the recommended dose. No harmful effects were noted in neonates at maternal exposures up to 9 times the human exposure.

In the PPND study there were two neonate deaths, likely as the result of viral infection, and for which a role for tildrakizumab could not be excluded. These occurred at an 85 fold margin of exposure. The weight of evidence does not suggest an increased risk of bacterial or viral infections with MK-3222.

2.3.4. Conclusion on non-clinical aspects

The non-clinical development program is considered sufficient to support the marketing authorisation of tildrakizumab in psoriasis patients.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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 4: Summary of Tildrakizumab Phase 1 Clinical Trials

Protocol	Short Description	Trial Design/Trial Population	Treatments (Number Randomized)	Efficacy and Safety Assessments
P05661/P004	Rising Single-Dose IV Trial in Healthy Subjects	Randomized, double-blind, placebo-controlled, rising single-dose trial in healthy subjects	0.1 mg/kg IV (N=4) 0.5mg/kg IV (N=4) 3 mg/kg IV (N=8) 10 mg/kg IV (N=6) Placebo IV (N=7)[‡]	• PK • PD (Total IL-23, IL-22, calprotectin) • ADA • Safety/tolerability
P05776/P005	Single-Dose SC Trial in Healthy Subjects	Randomized, double-blind, placebo-controlled, rising single-dose trial in healthy subjects	50 mg SC (N=14)[§] 200 mg SC (N=14)[§] Placebo SC (N=9)	• PK • PD (Total IL-23, IL-22, calprotectin) • ADA • Safety/tolerability
P06306/P007	Ethnic Sensitivity Trial	Two part, open-label, non-randomized, single-dose trial in Japanese, Chinese, and White[†] healthy subjects	Part 1: 50 mg SC (N=8, Japanese) 50 mg SC (N=7, White) 50 mg SC (N=4, Chinese) 200 mg SC (N=6, Japanese) 200 mg SC (N=6, White) 200 mg SC (N=4, Chinese) 400 mg SC (N=8, Japanese) 400 mg SC (N=6, White) 400 mg SC (N=4, Chinese) Part 2: 10 mg/kg IV (N=6, Japanese)	• PK • PD (Total IL-23) • ADA • Safety/tolerability

Protocol	Short Description	Trial Design/Trial Population	Treatments (Number Randomized)	Efficacy and Safety Assessments
P05382/P001	Rising Multiple-Dose IV Trial in Subjects with Psoriasis	Three part, rising multiple-dose, randomized, placebo-controlled, double-blind trial in subjects with moderate-to-severe plaque psoriasis	Part 1 (Day 1, 56, and 84): 0.1 mg/kg IV (N=3) 0.5 mg/kg IV (N=3) 3 mg/kg IV (N=7) ‡ 10 mg/kg IV (N=6) Placebo IV (N=6) Part 2 (Day 1, 28, and 56): 3 mg/kg IV (N=15) 10 mg/kg IV (N=14)‖ Placebo IV (N=11)¶ Part 3 (Day 1, 56, and 84): 0.05 mg/kg IV (N=6) 0.1 mg/kg IV (N=3) Placebo IV (N=3)	• PK • PD (PASI, Biomarkers) • ADA • Safety/tolerability
P009	Effect on CYP450 Isoenzymes and the Relative Bioavailability of two Tildrakizumab Product Images	Randomized, fixed-sequence, 2-Period, parallel-group, open-label, multiple-dose trial in subjects with moderate-to-severe psoriasis	Treatment A (N=10): Period 1: CYP450 cocktail# (Day 1) Period 2: 200 mg SC (via PFS on Day 1 and Day 29) with CYP450 cocktail (Day 57) Treatment B (N=10): Period 1: CYP450 cocktail# (Day 1) Period 2: 200 mg SC (via AI) on Day 1 and Day 29 with CYP450 cocktail (Day 57)	• PK (CYP450 probe substrates for CY3A4,CYP2C9,CYP1A2, CYP2C19 and CYP2D6) • PK (tildrakizumab via PFS vs AI) • PD (biomarkers) • ADA • Safety/tolerability
P05839/P006	Safety and Pharmacokinetic Trial in Subjects with Active Crohn's Disease	Randomized, placebo-controlled, multi-site, third-party blind trial in subjects with Crohn's Disease	0.5mg/kg IV (N=6) 3 mg/kg IV (N=6) 10 mg/kg IV (N=6) Placebo IV (N=6)	• PK†† • PD†† • ADA†† • Safety/tolerability

2.4.2. Pharmacokinetics

Original PK studies

Five Phase 1 trials performed by the applicant are presented to demonstrate the pharmacokinetic characteristics of tildrakizumab (summary description of studies in table above).

The Phase 1 program was conducted in 222 subjects, including 125 healthy subjects and 97 subjects with moderate to severe psoriasis. Fifty-nine (59) healthy male subjects and 66 healthy female subjects were included in the Phase 1 program, along with 74 male subjects and 23 female subjects with moderate to severe psoriasis. One hundred and three (103) healthy subjects were administered at least one dose of tildrakizumab and 15 healthy subjects were administered matched placebo. Across trials, healthy subjects received tildrakizumab via IV infusion over 1 hour at doses ranging from 0.1 milligram (mg)/kilogram (kg) to 10 mg/kg, or via SC administration at doses ranging from 50 to 400 mg. Seventy-five (75) subjects with psoriasis were administered at least one dose of tildrakizumab and 20 subjects with psoriasis were administered matched placebo. Repeat SC dosing with 200 mg tildrakizumab via PFS (Study P009) was also evaluated in the Phase 1 program.

During the Phase 2 & 3 programme, the applicant performed sparse PK sampling across their Phase 2b and their 2 pivotal Phase 3 studies. Pharmacokinetic data from these studies were pooled with data from the Phase 1 studies for analysis via population PK modelling.

Tildrakizumab is a humanized immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin 23 (IL 23) with high specificity and affinity. The binding characteristics, in vitro efficacy and specificity of tildrakizumab have been tested in a non-clinical pharmacology developmental program. The mechanism of action of tildrakizumab is the neutralization of human IL-23 thus inhibiting the IL-17 mediated immune response by the T helper 17

lymphocytes (Th17L). The mechanism of action was going to be justified in humans and several cytokine tissue and serum levels.

Three formulations (lyophilised and liquid) were used in the clinical development of tildrakizumab. Phase 1 trials (P05661, P05776, P06306, and P05382) and Phase 2b trial (P05495) and all trials with healthy subjects were conducted using a lyophilized formulation, whereas the Phase 1 trial (P009) and Phase 3 trials (P010 and P011) were conducted using the solution housed in a PFS. In P009, different modes of application (sc via syringe vs. sc via autoinjector) were evaluated.

The applicant has outlined the bioanalytical methods used to profile serum levels of IL23, IL22, IL6, TNFa and IL1B in Phase 1 and 2 studies. With the exception of total IL-23, commercially available kits were used to assay these biomarkers and a summary of the assay characteristics and validation status and have therefore been provided. In brief, the sensitivity and precision of these assays have been reported and are acceptable. A full validation report has been included for the IL-23 method and shows the assay can accurately quantitate IL-23 in normal human serum in the range of 20 - 43,740 pg/ml.

Tildrakizumab and anti-tildrakizumab antibodies in all these studies were assayed with sensitive and specific immunoassays methods. Bioanalytical methods have been adequately validated. The methods to measure unbound tildrakizumab, ADAs and Nabs in human serum were developed and originally validated at Merck, Union, NJ, USA. The methods were then transferred and validated at Covance, Chantilly, VA, USA (Phase 1 clinical trial P009, Phase 2b clinical trial P05495, and pivotal Phase 3 clinical trials P010 and P011). The method transfer validation demonstrated acceptable performance. The clinical documentation is detailed, compliant with regulatory expectations and considered as a trustworthy source of information.

Population PK analysis

Supporting the PK characterization of tildrakizumab is a POP PK analysis in 2098 subjects providing 17,321 evaluable concentration measures, using the specific assay of tildrakizumab, based on densely sampled PK data from Phase 1 (84 healthy and 19 subjects with psoriasis), as well as sparsely sampled PK data from Phase 2b (348 subjects with psoriasis) and Phase 3 (1646 subjects with psoriasis). The POP PK analysis included covariate analyses to inform intrinsic and extrinsic factor effects. E-R modelling of Week 12 PASI response and longitudinal PK-PD modelling of PASI response time-course in 1883 subjects with psoriasis from the Phase 2b and 3 trials allowed for evaluation of the impact of intrinsic and extrinsic factors on PASI response and assessment of the clinical comparability bounds. In combination with exposure-safety evaluations, these models were used to establish the potential need for dose adjustments in sub-populations.

Overall, the PK properties of tildrakizumab are very similar to other human IgG1-type immunoglobulin-based mABs with few specific characteristics:

Absorption

The subcutaneous formulation of tildrakizumab showed an absolute bioavailability ranging from 73% (90% CI: 46% - 115%, 200 mg SC vs. 3 mg/kg IV) to 80% (90% CI: 62% - 103%, 50 mg SC vs. 0.5 mg/kg IV) in healthy subjects, as a result of cross study single dose comparison. Maximum concentration was reached at 6.2 days after injection. Population PK analysis indicated a 31% higher bioavailability in healthy subjects compared to patients.

At steady state, following administration of 100 mg of tildrakizumab in subjects with moderate to severe plaque psoriasis geometric means (% CV) of AUC_{0-T} and C_{max} values were respectively 305 µg·day/mL (41%) and 8.1 µg/mL (34%), whereas they were 612 µg·day/mL (40%) and 16.3 µg/mL (33%) following administration of 200 mg.

Distribution

Tildrakizumab has limited extravascular distribution with volume of distribution (Vd) values ranging from 76.9 to 106 mL/kg.

Metabolism

Tildrakizumab is catabolized by general protein degradation processes. Small molecule metabolic pathways (E.g. CYP, glucuronosyltransferases) do not contribute to clearance. Small-molecule metabolic pathways (e.g., CYP450 enzymes, glucuronosyltransferases) do not contribute to its clearance.

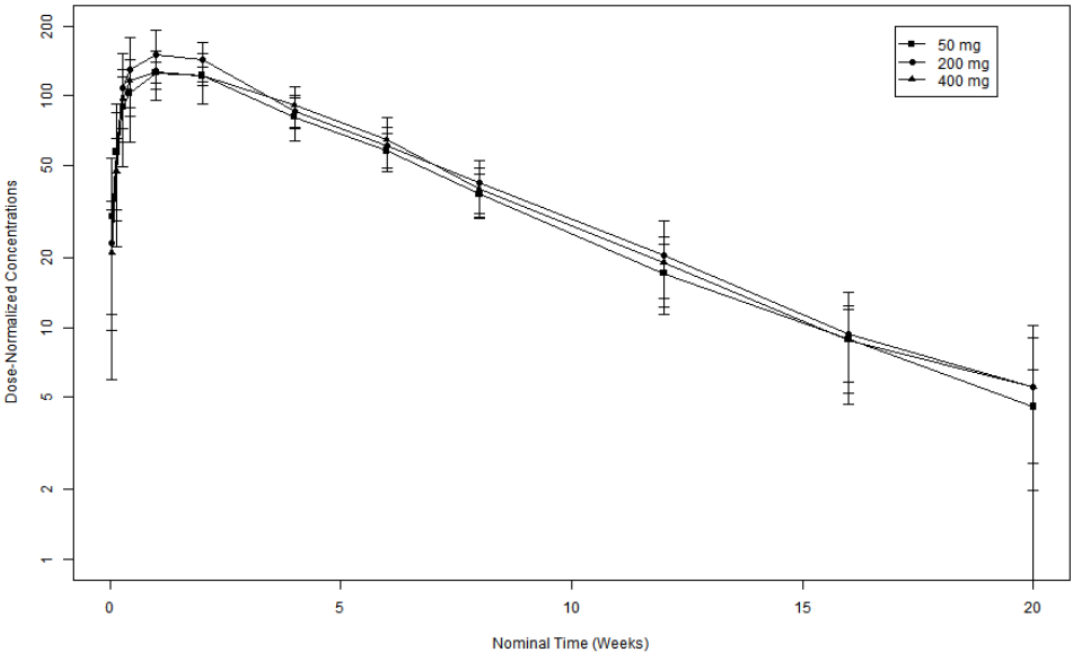
Excretion

Clearance values range from 2.04 to 2.52 mL/day/kg and the half-life was 23.4 days (23% CV) in subjects with plaque psoriasis.

Dose proportionality and time dependency

The POP PK model did not detect a departure from dose-proportionality across a wide range of doses. Based on simulations from the POP PK model, it was found that both AUC and Cmax at steady-state doubled with doubling of dose in psoriasis subjects.

Figure 3: Exposure in Healthy Subjects Following 50, 200 and 400 mg Single Dose Subcutaneous Administration of Tildrakizumab. PK profiles are dose normalized (Study P06306/P007)



Steady-state (SS) is achieved by 16 weeks with the clinical regimen (dosing on Week 0 and Week 4 and Q12W thereafter) with 1.1-fold accumulation in Cmax (maximum tildrakizumab concentration).

Steady-state treatment with 100 mg SC tildrakizumab results in geometric means (%CV) of AUC0-Week12 (Area under the concentration versus time curve from time zero to week 12) and Cmax of 305 µg•day/mL (41%) and 8.1 µg/mL (34%), respectively.

Steady-state treatment with 200 mg SC tildrakizumab results in geometric means (%CV) of AUC0-Week12 and Cmax of 612 µg•day/mL (40%) and 16.3 µg/mL (33%), respectively. Time to maximum concentration (Tmax) was 6.2 days (46%) for both dose groups.

Influence of TMDD could not be observed in the data.

Figure 4: Tildrakizumab serum concentration [arithmetic mean (SD)] versus time by dose group: Phase 2b study (Study P05495/P003)

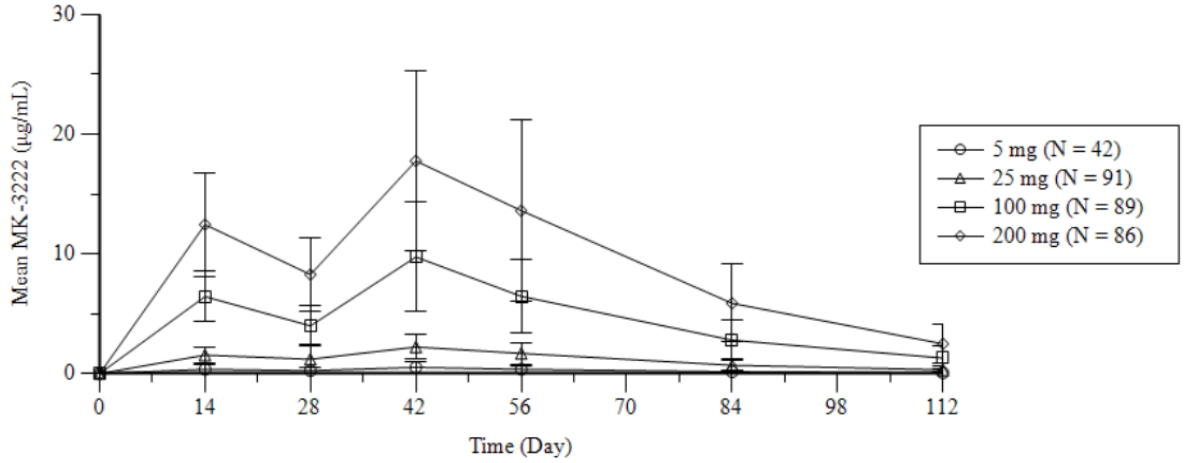


Figure 5 a: Tildrakizumab Serum Concentration-Time Profiles for the Phase 3 Studies. Subjects with Psoriasis Receiving Doses at Week 0 and Week 4 Followed by Q12W Dosing

1. Study P010

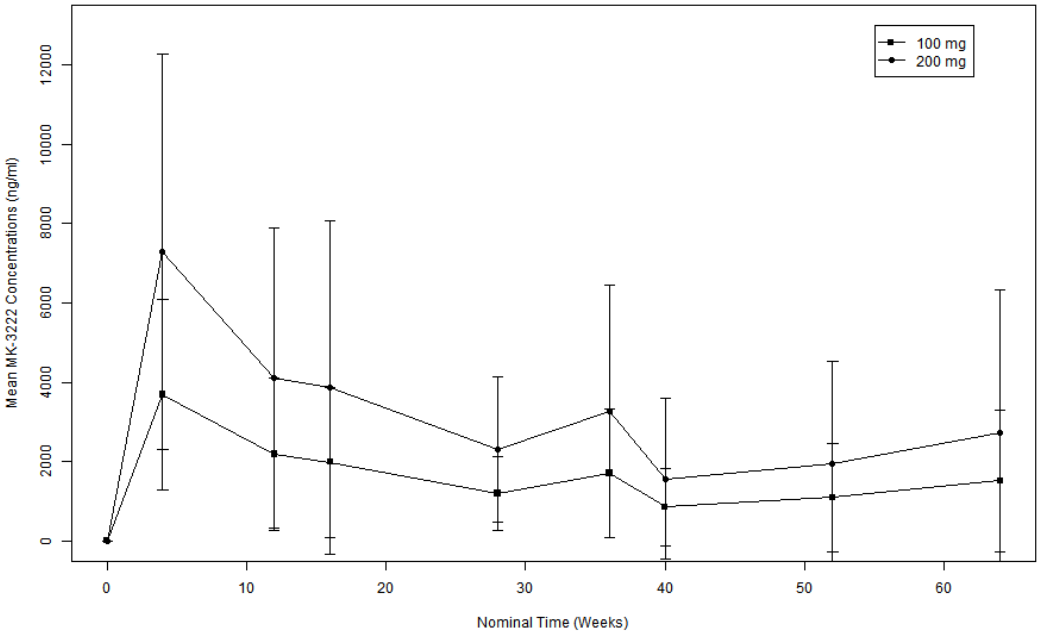
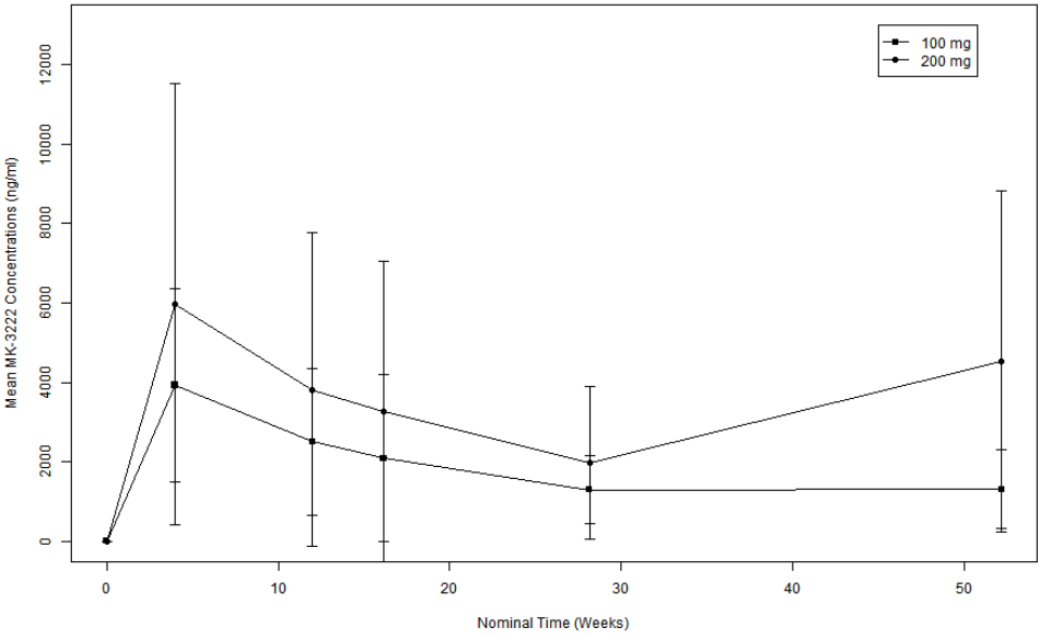


Figure 5 b:

2. Study P011



Intra- and inter-individual variability

Tildrakizumab PK exhibited moderate variability within and across individual clinical trials. PK samples showed a high variability arising mainly from the influence of body weight ant patient status. Simulations from the POP PK model indicated an inter-individual variability of 33-41% CV.

Intra-subject variability was explicitly assessed in Phase I trial P009 in subjects with psoriasis, where CV of the geometric means for Day-1 AUC0-Week12 and Cmax were 42 and 43%, respectively.

In addition to the PK parameter estimates, geometric means and %CV were calculated for CL, V, KA and derived PK parameters such as the absorption and elimination half-life. These calculations were based on posthoc parameters of the final run. Psoriatic subjects were characterized by a geometric mean (%CV) clearance of tildrakizumab of 0.32 L/day (38%), volume of distribution of 10.8 L (24%), absorption and elimination half-life (t½) of 1.5 days (18%) and 23.4 days (23%), respectively. Of note is the much lower CV of KA and absorption half-life, caused by the shrinkage of IIV on KA. Two of the three Phase 1 trials were conducted in healthy subjects.

Pharmacokinetics in the target population

The PK profile of tildrakizumab is consistent with that of other human mAbs which typically have low clearance (CL) and a limited volume of distribution (V).

Posthoc PK parameters for the psoriasis subjects in the Phase 2b and Phase3 trials generated from a one-compartment POP PK model indicated a geometric mean (% coefficient of variation (CV)) apparent CL (CL/F) of 0.32 L/day (38%), apparent volume of distribution (Vz/F) of 10.8 L (24%), absorption half-life and apparent elimination half-life (t1/2) of 1.5 days (18%) and 23.4 days (23%), respectively, and an absorption lag-time (Alag) of 1.2 hours. Standard diagnostic plots were generated to evaluate the adequacy of the base and final covariate models.

Simulated Derived PK Parameters for 100mg and 200mg Dose Groups

Since very few rich profiles were available in the psoriatic subject population (Trial P009) and none at the clinical dose of 100 mg, derived PK parameters such as AUCss, Cmax and tmax were obtained through simulation. Simulations were based on the demographics of all psoriatic subjects in the PK data set (Trials P05495, P009, P010 and P011) that received 100 mg or 200 mg tildrakizumab, respectively. The geometric mean values and %CV from this analysis are presented in the Table below. At steady state (SS) of treatment with 100 mg SC tildrakizumab, geometric means (%CV) of AUC0-tau and Cmax were 305 µg*day/mL (41%) and 8.1 µg/mL (34%), respectively. The corresponding figures for treatment with 200 mg SC tildrakizumab at SS are 612 µg*day/mL (40%) and 16.3 µg/mL (33%) for AUC0-tau and Cmax respectively. Tmax was 6.2 days (46%) for both dose groups. Tildrakizumab has moderate PK variability (33-41% CV for AUC0-tau and Cmax).

A significant difference in PK between healthy subjects and psoriasis subjects was observed. The sponsor states that body weight partially explains this discrepancy. Given the body weight distribution in both patients groups, this can be supported to some degree, however the introduced covariate HV on bioavailability accounts for almost the entire difference in bioavailability between healthy subjects and patients.

Pharmacokinetics in special populations

No pharmacokinetic studies have been conducted in special populations (ie pediatric [<18 years of age], elderly, subjects with renal or hepatic impairment). Results from population PK analyses indicate that age, serum albumin, creatinine clearance (CRCL), race (Asian, other), ethnicity (Hispanic), gender, body weight, formulation (Ph 1&2), patient status – all statistically significant- and prior treatment of psoriasis with a biological, Japanese origin did not have a clinically relevant effect on the CL/F of tildrakizumab. All evaluated intrinsic and extrinsic factors were within the clinical comparability bounds of 0.7-2.7. The impact of covariate effects are small (such as gender, race or ethnicity) to modest (body weight). The most influential covariates were body weight and subject population (healthy subjects vs psoriatic patients) on bioavailability with higher bioavailability in healthy subjects. High body weight (> 90 kg) was near the lower clinical bound. The potential for dose adjustment for higher body weight was evaluated using exposure-response and PK-PD models.

Most covariate effects were minor and did not lead to a visible improvement of model diagnostics. Inclusion of additional covariates on top body weight and subject population (both part of the base model) had little effect on inter-individual variability (IIV CL decreased by 3%, other IIVs unchanged) and no effect on residual error estimates. The lack of PK studies in special patient groups was found acceptable on the ground that tildrakizumab pharmacokinetics shows the general features of other IgG based mABs and previous regulatory and therapeutic experiences with these drugs do not warrant these studies. Introduction of covariates towards the final model has led to only a minor reduction of IIV values.

Pharmacokinetic interaction studies

Concomitant use of systemic corticosteroids and prior treatment of psoriasis with a biological agent were considered as potential covariates on the PK of tildrakizumab in the POP PK analysis. However, concomitant corticosteroids could not be formally tested as a covariate in the POP PK model because the predefined minimum of 50 subjects treated with systemic corticosteroids for at least 8 weeks was not met.

Prior treatment of psoriasis with a biological agent was tested but did not have a statistically significant influence on tildrakizumab exposure. In the E-R and longitudinal PK-PD models PASI75 response rates were similar in subjects regardless of prior treatment of psoriasis with a biological agent.

Based on the established POP PK model, tildrakizumab PK in subjects with and without these extrinsic factors was simulated using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting AUCss GMRs [90% CI] for subjects with/without concomitant systemic corticosteroids receiving 100 mg and 200 mg SC were 0.96 [0.80-1.14] and 1.02 [0.82-1.26], respectively. The resulting AUCss GMRs [90% CI] for subjects with/without prior treatment of psoriasis with a biological agent receiving 100 mg and 200 mg SC were 0.90 [0.85-0.95] and 0.89 [0.85-0.84], respectively.

Given the data and simulations provided, no clear influence of concomitant use of systemic corticosteroids and prior treatment of psoriasis with a biological agent could be detected. Of note, AUCss values for 100 mg and 200 mg doses in psoriasis subjects with concomitant systemic corticosteroids are very low (n= 11 and n=8).

The influence of tildrakizumab on the PK of CYP substrates (caffeine, warfarin, omeprazole, dextromethorphan and midazolam) was investigated by the applicant. Substrates have been administered as a cocktail, for the evaluation of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 metabolism. The largest effect could be detected on dextromethorphan (CYP 2D6 substrate), as AUC0-inf after a 30 mg dose of the substrate was 20% higher compared to the AUC0-inf without parallel tildrakizumab administration (two doses SC administered 4 weeks apart). Similarly, AUC0-inf of Caffeine (CYP 1A2 substrate) following a 200 mg dose was 14% higher; AUC0-inf of Midazolam (CYP 3A4 substrate) after a 2 mg dose was 11% higher, AUC0-inf of S-warfarin (CYP 2C9 substrate) following a 10 mg dose was 7 % higher, respectively. No effect on Omeprazole (CYP 2C19 substrate) could be detected.

It is expected that tildrakizumab has low interaction potential based on the in-vitro data and similarity of tildrakizumab to other monoclonal antibodies.

2.4.3. Pharmacodynamics

Mechanism of action

Tildrakizumab (also known as MK-3222 and SCH 900222) is a high affinity (297 picomolar (pM)), humanized immunoglobulin G1/kappa (IgG1/κ) antibody that specifically binds to p19 subunit and neutralizes human IL-23. IL-23 is a heterodimeric cytokine consisting of a unique p19 subunit and a common p40 subunit shared with IL-12. It has been recognized as a key driver of autoimmunity in mouse models and human diseases, which is commonly attributed to the ability of IL-23 to polarize and activate Th17 cells, a subset of T cells that has been identified as having a central role in autoimmunity.

Regarding psoriasis pathogenesis, the IL23/Th17 pathway is considered to have a significant role in psoriasis pathogenesis. Genome wide association studies (GWAS) have identified psoriasis risk alleles around gene regions that encode IL-23 (IL23A, IL12B) and the IL-23R. Both p19 and p40 subunits of IL-23 are over expressed in psoriatic skin lesions, while the unique p35 subunit of IL-12 is not. Th17 cells, and the cytokines they produce, are abundant in psoriasis lesions, where they exert pro-inflammatory and pro acanthotic effects. Studies have also indicated that disease improvement with TNF-α inhibitor therapy correlated with the rapid down-modulation of IL- 23 and Th17 cell products, and successful response to treatment was dependent on the inactivation of the IL-23/Th17 pathway. Recent data suggest that the efficacy of these antagonists likely depends primarily, if not exclusively, on their ability to neutralize IL-23 rather than IL-12, thus this provides the rationale for selectively targeting IL-23p19 in patients with psoriasis.

Primary pharmacology

Psoriasis is a chronic inflammatory skin disease. Data suggest that the efficacy of interleukin (IL)-12/IL-23 biological agents depends on the ability to neutralize IL-23 rather than IL-12. Therefore, an approach to the treatment of moderate-to-severe chronic plaque psoriasis may be the use of a humanized anti-IL-23p19 monoclonal antibody.

Decreases in PASI score demonstrated favourable tildrakizumab activity in Phase 1 trials (P05382 and P009).

Various exploratory biomarkers of disease activity and safety were evaluated in early clinical trials for potential dose-response and/or predictiveness of PASI response: PASI, total IL-23, IL-22, Calprotectin, skin biopsies, IL-6 and high-sensitivity C-reactive protein (hsCRP). Biomarkers of safety: Across the Phase 1 program, IgG, IgE, IgA, IgM, and ESR were analysed as exploratory biomarkers of immunogenicity and inflammation. There were no clinically meaningful changes in these parameters.

No useful biomarkers of target engagement (total IL-23), dose response or activity (IL-22, calprotectin) were identified. For example, total IL-23 was anticipated to increase when tildrakizumab bound IL-23; however, concentrations were largely undetectable pre-and post- treatment with tildrakizumab.

Serum IL-6, TNFα, IL-1β was explored in P05382 to ensure there was no immune stimulation, and there were no clinically meaningful changes in these parameters.

Secondary pharmacology

Overall, provided data indicate no statistically or clinically significant effect of tildrakizumab on QTc interval.

Immunogenicity

The integrated ADA data through 12-16 weeks included subjects treated with 100 mg (N=700) or 200 mg (N=700) tildrakizumab. The integrated ADA incidence through 52-64 weeks was summarized for evaluable subjects who were treated continuously with 100 mg (N=400) or 200 mg (N=380) in Phase 2b and Phase 3 for 52-64 weeks. For subjects in Phase 2b and Phase 3 dosed with 100 mg, the proportion of TE-POS subjects increased over time from 4.3% through 12-16 weeks to 6.5% through 52-64 weeks. In addition, the proportion of subjects who were TE-POS and NAb-POS was 0.6% (4 of 700) through 12-16 weeks and 2.5% (10 of 400) through 52-64 weeks [Table 2.7.2: 14], [Table 2.7.2: 15]. A similar proportion of subjects dosed with 200 mg was TE-POS was 4.1% (29 of 700) through 12-16 weeks and 8.2% (31 of 380) through 52-64 weeks. In addition, the proportion of subjects who were TE-POS and NAb-POS was 0.6% (4 of 700) through 12-16 weeks and 3.2% (12 of 380) through 52-64 weeks.

Antibodies to Tildrakizumab and Efficacy

There was no effect of ADA status, positive or negative/inconclusive, on the proportion of subjects achieving the primary and key secondary endpoints of PASI and PGA response at Week 12. Only TE-POS NAb-POS subjects showed a minor impact in clinical response. The clinical response in subjects in other ADA positive categories was similar to that of subjects in the ADA negative category.

The overall incidence of antibodies against tildrakizumab was low (4.2% through 12-16 weeks and 7.3% through 52-64 weeks.). A number of samples were classified as inconclusive however this did not impact the final conclusion. Efficacy seems not be influenced by the antibodies. For detailed analysis, please, refer to the efficacy and safety sections in this report.

There were no clinical studies designed and conducted to evaluate pharmacodynamic interactions with other medicinal products.

No genetic differences have been evaluated by the Applicant.

Relationship between plasma concentration and effect

An efficacy E-R analysis was conducted across Phase 2b and Phase 3 (P05495, P010 and P011) to investigate the relationship between tildrakizumab exposure and PASI response at Week 12 to assess the suitability of 100 and 200 mg SC as clinical doses.

The primary clinical endpoint was defined at Week 12, but PASI was assessed throughout all trial Parts (Week 0, 4, 8, 12, 16, 22, 28, 32, 36, 40, 44, 48, 52, 56, 60 and 64). At the end of Part 2, subjects were assessed for PASI response and based on PASI improvement were defined as Responder (PASI improvement ≥75%), Partial Responder (≥ 50% and <75%), Non-Responder (<50%) followed by subsequent re-randomization for Part 3.

Compared to 100 mg, 200 mg evoked a slightly more robust response regarding PASI 90 responses towards the end of the clinical trial, but overall both doses could be considered comparable. A strong exposure-efficacy trend could be detected: Similarly, PASI response increases from exposure (Cav12) Q1 to Q4 regarding each of the doses individually.

Exposure-efficacy relationships:

The final exposure-efficacy model (emax model) included WEIGHT and AGE as covariate on E0. A strong exposure-efficacy response is detected, whereas (simulated) dose-efficacy relationship (100mg vs 200 mg; 200 mg vs 400 mg) was rather flat.

A high exposure/ bodyweight – efficacy relationship is detected, in contrast to a flat dose-efficacy relationship (dose 100mg, 200mg, 400mg) as showed be simulations. Body weight has a very high impact on exposure (lowered) and also on PASI response (effect lowered). High bodyweight was constantly correlated with decreased tildrakizumab exposure and decreased PASI response throughout all simulated dosing regimens (0, 25, 100, 200, 400 mg). Higher dosing (400mg) would result only in a minor gain in benefit based simulations using the E-R model. Thus the sponsor was asked to discuss potential factors that trigger this pronounced loss in efficacy in patients at high body weight. The potential IIV in F should be considered. Instead of a separate estimation of F in the patient population by including IV data, detailed information on F regarding differences between healthy subjects and patients, and variability among patients from population PK analysis was provided upon CHMP request. The sponsor was also asked to simulate a dosing regimen where 200 mg or 100 mg would be administered more frequently. Simulations indicated that maximum efficacy is mostly reached following the envisaged dosing regimen.

Covariate AGE, like WEIGHT was found to influence exposure – efficacy with regard to PASI response in the exposure-response model. Therefore, the applicant was asked to provide a subgroup analysis analogously. Analyses regarding age indicated that no dose adjustment is warranted on the basis of age. Subgroup analysis regarding covariate WEIGHT also showed that exposure in terms of AUCss following 100 mg Q12W for patients ≤ 90 kg and following 200 mg Q12W for patients > 90 kg will be more balanced across the patient population.

Dose/Exposure-safety relationship

A safety evaluation of 100 mg vs 200 mg in partial responders during Part 3 of P010 and P011 has been conducted. Safety was assessed by summarizing the proportion of subjects with certain Adverse Events (AE)/Adverse Event Categories (infections/infestations, severe infections/infestations, upper respiratory tract infections (URTI) and nasopharyngitis, basal/squamous cell carcinoma, melanoma,

MI/ischemia, cardiac failure, drug hypersensitivity). When comparing placebo, 100 mg, and 200 mg in all subjects in Part 1 of P010 and P011, no specific safety difference was observed. Similarly, when comparing 100 mg with 200 mg across Part 1 and Part 2 combined, no apparent differences were seen. Sub-setting this latter comparison in lower vs higher body weight subjects (>90 kg and >120 kg) did not suggest any differential safety signal between the doses or compared to the integrated data. The lack of a differential safety profile with body weight was further confirmed in a subgroup analysis in the Phase 2b/3 placebo-controlled safety pool.

An assessment was made of observed AEs by dose in Part 3 partial responders of trials P010 and P011, who initially started on the 100 mg regimen and were randomized to either 100 mg or 200 mg at Week 28. During Part 3, there was a numerically greater percentage of subjects with infections/infestations in partial responders were uptitrated to 200 mg compared to those who continued to receive 100 mg. The number of partial responders was low (N=40 per group).

Various AE categories were evaluated as part of the exposure-safety assessment (Any AE, infection, severe Infection, URTI, malignancies, non-melanoma skin cancer, melanoma skin cancer, confirmed extended Major Adverse Cardiac Events (MACE), drug-related hypersensitivity). None of these AE categories indicated a specific safety signal between the observed exposure quartiles. No clear dose-safety relationship exposure-response relationship with regard to safety could be detected.

2.4.4. Discussion on clinical pharmacology

The MAH proposed dose for this product was 200 mg administered subcutaneously at weeks 0, 4 and every 12 weeks thereafter. Intravenous and subcutaneous doses including the MAH proposed 200 mg doseas well as higher than the proposed dose have been evaluated in a large number of healthy volunteers and patients with psoriasis. Additionally, a population PK analysis has been conducted using densely and sparsely sampled PK data from phase 1, 2 and 3 trials of tildrakizumab. The exposure across the clinical development programme is considered adequate for PK and safety characterisation of tildrakizumab. Additionally, no significant differences were seen in adverse events in subgroup analyses (stratified by dose administered, patient weight etc).

The PK profile of tildrakizumab is consistent with that of other human mAbs, which typically have low clearance and a limited volume of distribution. The POP PK analysis indicated that psoriatic subjects were characterized by a geometric mean (%CV) clearance (CL/F) of tildrakizumab of 0.32 L/day (38%), volume of distribution (V/F) of 10.8 L (24%), absorption and elimination half-life (t½) of 1.5 days (18%) and 23.4 days (23%), respectively, and an absorption lag time of 0.05 days (1.2 hours).

Based on simulations, it was determined that at steady state (SS) of treatment with 100 mg SC tildrakizumab, geometric means (%CV) of AUC0-tau and Cmax are 305 µg*day/mL (41%) and 8.1 µg/mL (34%), respectively. The corresponding numbers for treatment with 200 mg SC tildrakizumab at SS are 612 µg*day/mL (40%) and 16.3 µg/mL (33%) for AUC0-tau and Cmax respectively. Tmax was 6.2 days (46%) for both dose groups. Tildrakizumab has moderate PK variability (33-41% CV for AUC0-tau and Cmax). The geometric mean (%CV) accumulation ratio was 1.1 (6%).

The longer term PK data presented in the dossier did not fully support the MAH's assertion that steady state is reached at week 16 with stable serum tildrakizumab concentrations thereafter. Additional experimental and simulated data as well as justification have subsequently been provided to demonstrate that serum tildrakizumab levels reach steady state after week 16 under the MAH initially proposed dosing regimen of 200 mg Q12W. Prior treatment of psoriasis with a biological was not detected as statistically significant covariate.

A population PK analysis indicated that all evaluated intrinsic and extrinsic factors were within the clinical comparability bounds of 0.7-2.7. These bounds have been defined based in both the 100 mg and 200 mg doses. The impact of covariate effects are small (such as gender, race or ethnicity) to modest (body weight).

The most influential covariates were body weight and subject population (healthy subjects vs psoriatic patients). High body weight (> 90 kg) was near the lower clinical bound. The potential for dose adjustment for higher body weight was evaluated using exposure-response and PK-PD models.

The applicant has demonstrated lower exposure of tildrakizumab in patients of higher weight. Exposure is shown to be dose proportional across the 100 mg and 200 mg dose within the weight brackets analysed. In addition, higher body weight was found to be correlated with decreased PASI response. Most covariate effects were minor and did not lead to a visible improvement of model diagnostics. Inclusion of additional covariates on top body weight and subject population (both part of the base model) had little effect on inter-individual variability (IIV CL decreased by 3%, other IIVs unchanged) and no effect on residual error estimates.

Exposure was noted to be significantly higher in healthy volunteers than in subjects with psoriasis. This was despite the fact that all healthy volunteers received the lyophilised formulation which was found to have a 5% lower relative bioavailability than the pre-filled syringe. The applicant argues that this is partially explained by body weight differences but no other causes have been proposed. The applicant has justified the unlikely disease effect on tildrakizumab exposure. However, bioavailability in patients remains unknown and was set and fixed to 100% in the population PK analysis. In consequence, population PK analysis suggests a bioavailability of 131% regarding healthy subjects, which is not plausible. It is agreed that the population PK analysis only served for assessing the data variability in general. However information about bioavailability in the target patient population and in comparison with healthy subjects has been reflected in the SmPC section 5.2.

There were no clinical studies designed and conducted to evaluate pharmacodynamic interactions with other medicinal products.

It is expected that tildrakizumab has low interaction potential based on the in vitro data and similarity of tildrakizumab to other mAbs.

The mechanism of action of tildrakizumab is the neutralization of human IL-23 through binding to its p19 subunit thus inhibiting the IL-17 mediated immune response by the T helper 17 lymphocytes (Th17L). The mechanism of action was going to be justified in humans and several cytokine tissue and serum levels.

Various exploratory biomarkers of disease activity and safety were evaluated in early clinical trials for potential dose-response and/or predictiveness of PASI response: PASI, total IL-23, IL-22, Calprotectin, skin biopsies, IL-6 and high-sensitivity C-reactive protein (hsCRP). Biomarkers of safety: Across the Phase 1 program, IgG, IgE, IgA, IgM, and ESR were analysed as exploratory biomarkers of immunogenicity and inflammation. There were no clinically meaningful changes in these parameters. Serum IL-6, TNFα, IL-1β was explored in P05382 to ensure there was no immune stimulation, and there were no clinically meaningful changes in these parameters.

The data provided indicate no statistically or clinically significant effect of tildrakizumab on QTc interval.

The immunogenicity of tildrakizumab was analysed. Additionally, all subjects positive for antibodies to tildrakizumab in Phase 2 and Phase 3 studies were assessed for the potential of these antibodies to neutralize the bioactivity of tildrakizumab (ie, NAbs) using a sensitive and drug tolerant competitive

ligand binding assay. The overall incidence of antibodies against tildrakizumab was low. Efficacy seems not to be influenced by the antibodies.

The most important issue arising from the clinical pharmacology studies is the potential issue of body weight on clinical response. By evaluating the dose-response in relation to efficacy 200 mg evoked a slightly more robust response regarding PASI responses. In contrast to the flat dose-response relationship, a strong exposure-efficacy trend could be detected: PASI response increases from exposure (Cav12) Q1 to Q4 regarding each of the doses individually.

While the population PK analysis showed a slight decrease in exposure with increased body mass, increased tildrakizumab exposure was not linked to greater clinical response.

The MAH proposed 200 mg dose has not been fully justified from an exposure-response perspective in the clinical pharmacology section of the dossier. Both observed data and the simulations indicate that at 100 and 200 mg maximum efficacy is mostly reached. The differentiation between the two doses regarding dose-response relationships remains very vague and becomes more apparent over time 52 and 64 weeks in terms of PASI, PGA scores and DLQI. There is a point that in lower weight patients < 90 kg the 100mg may be sufficient dose, as body weight was identified as most influential covariate on tildrakizumab PK. Supportively, from the pharmacokinetic point of view, subgroup analysis regarding covariate weight indicates that exposure in terms of steady state AUCss following 100 mg Q12W for patients ≤90 kg and following 200 mg Q12W for patients > 90 kg will be more balanced across the patient population. Similar trends were indicated by a detailed subgroups analysis of efficacy endpoints with respect to body weight bins.

Thus, proposing an optimal dosing regimen that will be adjusted to body weight (90kg) is considered appropriate.

Therefore the CHMP considered that 100mg was the most relevant regimen and did not agree with the applicant proposal of 200mg dose. An alternative dose regimen of 200mg seem however plausible in higher weight patients with a cut off of more than 90 kg. A more flexible dose in the SmPC section 4.2 was the preferred option based on the above data and therefore recommended by CHMP.

The results are reflected in section 5.1 and 5.2 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The applicant has provided an acceptable review of the pharmacology of this medicinal product. The pharmacokinetic profile of the product has been well characterised. The MAH initially proposed dose was discussed during the whole application. Ultimately the CHMP concluded that the optimal dose would be 100 mg and that in specific situations (patients with higher weight more than 90 kgs and patients with high burden disease) the dose of 200mg may be used.

In patients with psoriasis tildrakizumab is slowly absorbed with median time to Tmax of approximately 6.2 days after SC injection. The mean terminal half-life (t1/2) value was estimated to be approximately 23 days in a population PK analysis. The most important issues arising from the clinical pharmacology studies are the potential issue of body weight on clinical response, disease effects on tildrakizumab exposure, and a clear justification of the proposed 200 mg dosing regimen. (please refer to additional discussion later in the report). The primary pharmacodynamics profile of the product has been adequately described. The immunogenicity data provided for the medicinal product are acceptable and in line with other IgG monoclonal antibodies. No apparent association between the development of antibodies to tildrakizumab and the occurrence of adverse events has yet been noted.

2.5. Clinical efficacy

The following clinical trials were performed to support the application.

Table 5 Summary of efficacy trials

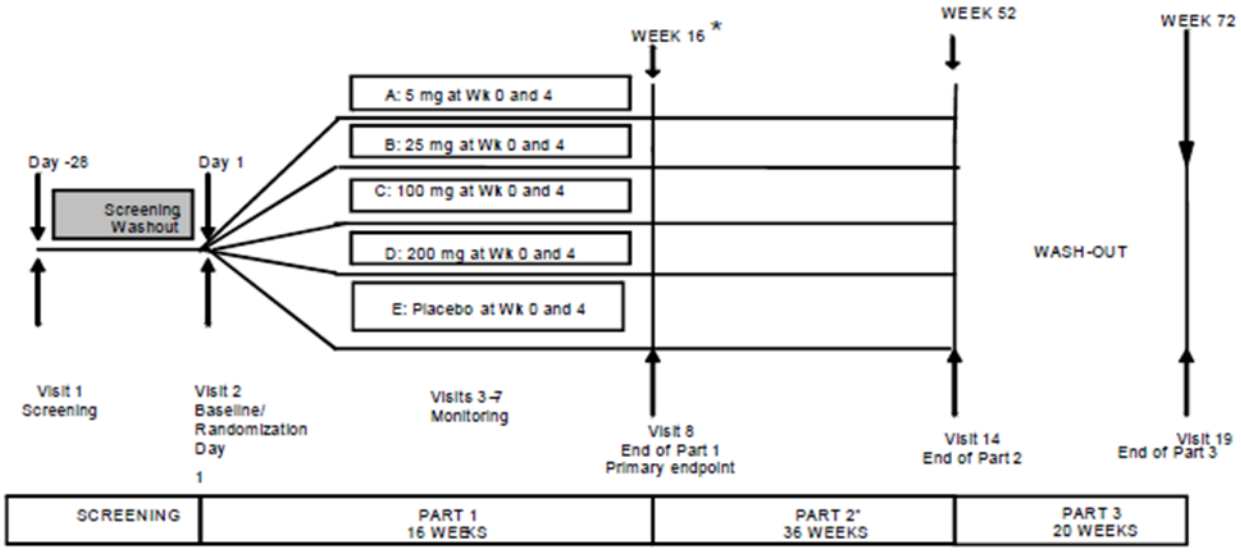
Protocol Number	Trial Population	Trial Design	Primary Objective(s)	Number of Subjects Randomized	Trial Status
Phase 2b Trial					
P05495 (P003)	Subjects with moderate-to-severe chronic plaque psoriasis	Randomized, double-blind, placebo-controlled, parallel-design, dose-range finding trial	To evaluate the optimal dose regimen of tildrakizumab (also known as SCH 900222 or MK-3222) to induce PASI 75 response at Week 16 in subjects with moderate-to-severe psoriasis.	Tildrakizumab 5 mg: 42 Tildrakizumab 25 mg: 92 Tildrakizumab 100 mg: 89 Tildrakizumab 200 mg: 86 Placebo: 46 Total: 355	Completed
Phase 3 Trials					
P010	Subjects with moderate-to-severe chronic plaque psoriasis	Randomized, double-blind, placebo-controlled, parallel-group trial with a long-term safety extension.	To assess the efficacy of tildrakizumab compared to placebo in the treatment of moderate-to-severe chronic plaque psoriasis as measured by the proportion of subjects with at least 75% improvement from Baseline in the Psoriasis Area and Severity Index (PASI 75 response) and the proportion of subjects with a Physician's Global Assessment (PGA) score of "clear" or "minimal" with at least a 2-grade reduction from Baseline at Week 12.	Tildrakizumab 100 mg: 309 Tildrakizumab 200 mg: 308 Placebo: 155 Total: 772	Base Trial Completed; Extension Ongoing
P011	Subjects with moderate-to-severe chronic plaque psoriasis	Randomized, double-blind, active-comparator and placebo-controlled, parallel-group trial with a long-term safety extension.	To assess the efficacy of tildrakizumab compared to placebo in the treatment of moderate-to-severe chronic plaque psoriasis as measured by the proportion of subjects with at least 75% improvement from Baseline in the Psoriasis Area and Severity Index (PASI 75 response) and the proportion of subjects with a Physician's Global Assessment (PGA) score of "clear" or "minimal" with at least a 2-grade reduction from Baseline at Week 12.	Tildrakizumab 100 mg: 307 Tildrakizumab 200 mg: 314 Etanercept: 313 Placebo: 156 Total: 1090	Base Trial Completed; Extension Ongoing

A total of 2217 patients were randomized in the tildrakizumab clinical development program consisting of 1 Phase 2b dose ranging study (P05495/P003) and 2 pivotal Phase 3 studies (P010 and P011). P05495 and P010 were placebo-controlled and P011 used etanercept as additional comparator. Efficacy variables used as endpoints were PASI 75, 90, 100 and PGA at different timepoints, while PASI 75 and PGA were used as co-primary endpoints in the pivotal endpoints.

2.5.1. Dose response study

The schematic representation of the study design of the dose response study (P05495/P003) is presented below:

Figure 6: study design



Study methods/objectives

The study P05495 consisted of screening/wash-out period followed by 3 Parts. Part 1 was a 16-week, double-blind, placebo-controlled, treatment period to evaluate the optimal dose regimen for induction of response (Weeks 0 to 16).

Randomisation

Patients were randomized to receive tildrakizumab 5 mg, 25 mg, 100 mg, 200 mg or placebo in a 1:2:2:2:1 ratio at Weeks 0 and 4. At Week 16 (end of part 1) treatment assignments were maintained or modified on PASI 75 response. Part 2 was a 36-week (Weeks 16 to 52), double-blind, treatment period to evaluate the optimal dose regimen for maintenance of response.

Patients received trial medication every 12 weeks for an additional 36 weeks during Part 2. Part 3 was a 20-week washout period (Weeks 52 to 72).

Inclusion/exclusion criteria

Adult male and female patients (≥18 years of age) with a diagnosis of moderate-to-severe chronic plaque psoriasis (defined by ≥10% body surface area [BSA] involvement, "moderate" or greater score on the PGA scale, and PASI score ≥ 12 at baseline) who are considered to be candidates for phototherapy or systemic therapy were eligible to participate in the trial. Excluded were patients with presence of non-plaque forms of psoriasis, any infection requiring treatment with systemic antibiotics within 2 weeks prior to Screening, positive HIV test result, hepatitis B surface antigen, hepatitis C test result, previous exposure to any agents targeting IL-12 and/or IL-23.

The study design and eligibility criteria were adequate for this dose response study. The baseline characteristics were similar between the treatment groups.

Primary endpoint

The primary endpoint shows the highest rate of PASI 75 response in the tildrakizumab 200 mg group followed by the tildrakizumab 100 mg group. These dosing groups also showed a meaningful difference to placebo with 67.65% for the 200 mg group and 56.23% for the 100 mg group. The other endpoints assessed in this study also supported these dosing regimens.

Figure 7: Analysis of Endpoint: PASI75 Response Rate at Week 16 for Part 1(Full Analysis Set)

PASI75 Responder

	5 mg N=42		25 mg N=90		100 mg N=89		200 mg N=86		Placebo N=45	
	n	%	n	%	n	%	n	%	n	%
Endpoint(Week 16)	14	33.33	58	64.44	59	66.29	64	74.42	2	4.44

Treatment Comparisons in PASI75 Response Rate (%)

	Difference(%) in PASI75 Response (95% C.I.)	P-Value
5 mg - Placebo	28.89(13.41, 44.36)	0.001
25 mg - Placebo	60.00(48.42, 71.58)	<0.001
100 mg - Placebo	61.85(50.33, 73.37)	<0.001
200 mg - Placebo	69.97(58.96, 80.99)	<0.001

Note: P-values are calculated using Cochran-Mantel-Haenszel (CMH) test stratified by Baseline weight (<=90 kg or >90 kg) and prior use of biologics for psoriasis (Yes/No). The missing PASI value is imputed by last non-missing postbaseline PASI value carried forward(LOCF) for any subject who has not discontinued due to lack of efficacy or loss of response, or used prohibited medications

Secondary Endpoint

The PGA response of clear or almost clear 0-1 was statistically significant better with Tildrakizumab treatment. The highest responses were seen with the 200mg dose, this was seen in the full analysis and per protocol sets.

Figure 8: Analysis of Endpoint: PGA Response Rate (Proportion of Subjects with PGA "cleared" or "minimal") at Week 16 For Part 1(Full Analysis Set)

PGA Responder

	5 mg N=42		25 mg N=90		100 mg N=89		200 mg N=86		Placebo N=45	
	n	%	n	%	n	%	n	%	n	%
Endpoint(Week 16)	14	33.33	52	57.78	55	61.80	64	74.42	1	2.22

Treatment Comparisons in PGA Response Rate (%)

	Difference(%) in PGA Response (95% C.I.)	P-Value
5 mg - Placebo	31.11(16.22, 46.00)	<0.001
25 mg - Placebo	55.56(44.48, 66.63)	<0.001
100 mg - Placebo	59.58(48.60, 70.55)	<0.001
200 mg - Placebo	72.20(62.02, 82.37)	<0.001

Note: P-values are calculated using Cochran-Mantel-Haenszel (CMH) test stratified by Baseline weight (<=90 kg or >90 kg) and prior use of biologics for psoriasis (Yes/No). The P-value for any active v.s placebo comparison is considered nominal and for informational purpose only if the corresponding P-value for the same comparison in PASI75 is not statistically significant at either Week 16 or Week 12. The missing PGA value is imputed by last non-missing post baseline PGA value carried forward (LOCF) for any subject who has not discontinued due to lack of efficacy or loss of response, or used prohibited medications.

Table 6: Proportion of Subjects with at least 2-points decreased from baseline and 0/1 values in PGA response, at Week 16 in P05495 (P003) study

Statistics	Placebo	5 mg	25 mg	100 mg	200 mg
PGA Response (Week 16)-Full Analysis Set					
Subjects with data (N)	N=45	N=42	N=90	N=89	N=86
Responders (%)	1 (2.22)	14 (33.33)	52 (57.78)	55 (61.80)	64 (74.42)
Difference in % vs placebo (95% CI) [a]		31.1 (16.2, 46.0)	55.6 (44.5, 66.6)	59.6 (48.6, 70.6)	72.2 (62.0, 82.4)
p-value [b]		0.0001	<0.0001	<0.0001	<0.0001
PGA Response (Week 16)-Per Protocol Population					
Subjects with data (N)	N=43	N=40	N=87	N=88	N=85
Responders (%)	1 (2.33)	13 (32.50)	51 (58.62)	54 (61.36)	64 (75.29)
Difference in % vs placebo (95% CI) [a]		30.2 (15.0, 45.4)	56.3 (45.0, 67.6)	59.0 (47.9, 70.2)	73.0 (62.8, 83.2)
p-value [b]		0.0003	<0.0001	<0.0001	<0.0001

Tildrakizumab has statistically significant higher response rates for PGA response (defined as “clear or minimal” with at least 2 point reduction from baseline) as compared to placebo. The PP analysis further supports the outcome of the analysis in the FAS population.

2.5.2. Main studies

The phase 3 clinical program for tildrakizumab consisted of 2 pivotal studies **P010 (reSURFACE1)** and **P011 (reSURFACE2)**. P010 was placebo-controlled, while P011 also used etanercept as active comparator. The doses of tildrakizumab were selected based on the results of the Phase 2 dose-ranging trial, P05495.

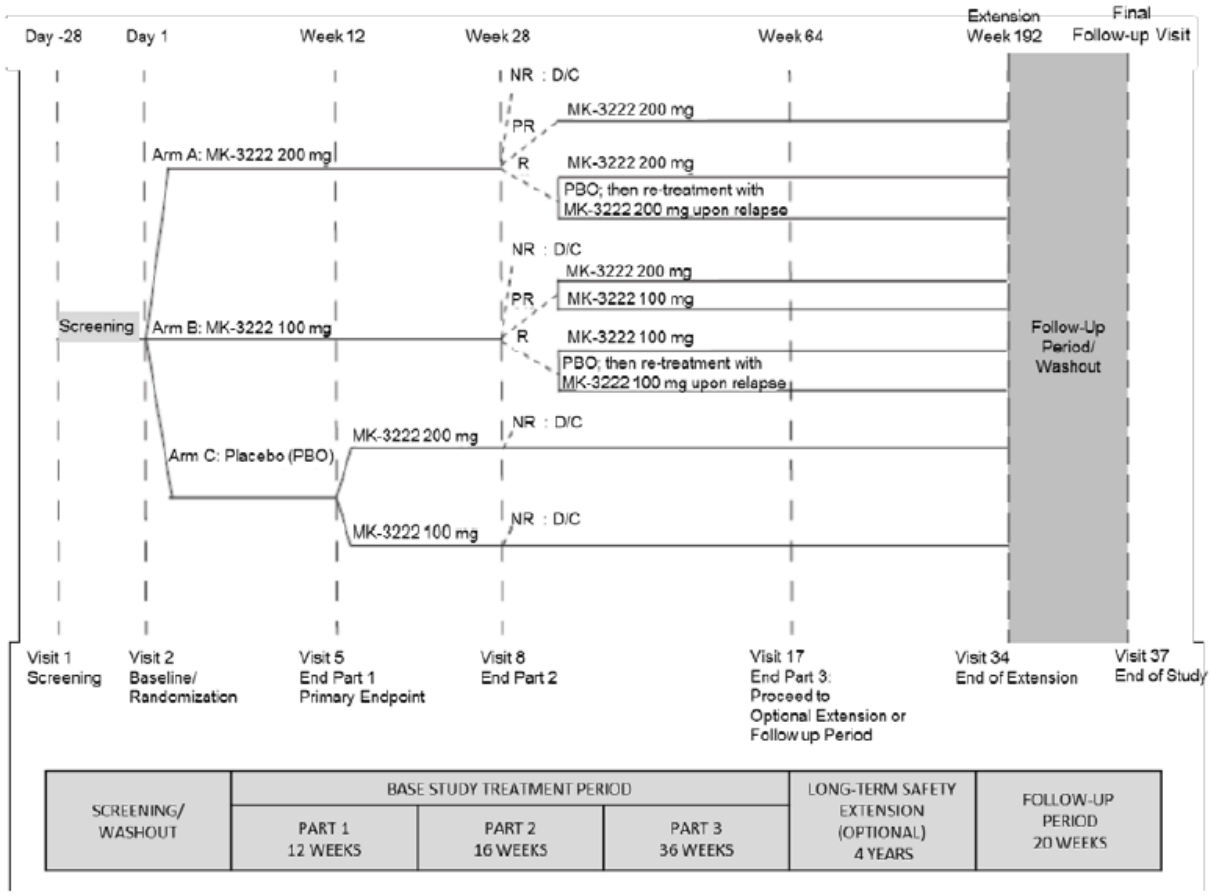
2.5.2.1. Study P010 (reSURFACE1)

Study P010 was a 64-week, Phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous Tildrakizumab, followed by an optional Long-Term Safety Extension Study, in patients with moderate-to-severe chronic plaque psoriasis.

Methods

The schematic description of the study is presented hereafter.

Figure 9: study design



NR were subjects who achieved <50% improvement in PASI response from baseline. At Week 28, NR were discontinued.
PR were subjects who achieved ≥50% but <75% improvement in PASI response from baseline.
R were subjects who achieved ≥75% improvement in PASI response from baseline.

D/C = discontinuation; NR = non-responders; PASI = Psoriasis Area and Severity Index; PR = partial responders; R = responders.

Study P010 consisted of a 4-week screening period, a 12-week Part 1 period (Week 0 to Week 12), a 16-week Part 2 period (Week 12 to Week 28), a 36-week Part 3 period (Week 28 to Week 64), an optional 4 year long term extension, and a 20-week follow-up period.

Objectives

The primary objectives were to demonstrate the efficacy and safety of tildrakizumab compared to placebo in patients with moderate-to-severe plaque psoriasis.

Study Participants

Patients selected were adult males and females 18 years of age or older with a diagnosis of plaque psoriasis for more than 6 months and were candidates for phototherapy or systemic therapy. Disease severity was gated to moderate to severe by baseline scores of BSA involvement ≥10%, PASI score ≥ 12, PGA of at least moderate disease (≥3). A maximum of 30% of patients may have had a diagnosis of psoriatic arthritis at baseline and a maximum of 40% of patients may have had prior exposure to biological therapies for psoriasis.

The exclusion criteria were designed to ensure patients safety. Excluded were patients with any infection including HIV, HCV and HBV, malignancies, hospitalization due to CV events within 6 months and other significant organ dysfunctions. Further were patients excluded who in the opinion of the investigator, were not be able to participate optimally in the trial as well as subject who, in the opinion of the investigator, had a history of alcohol or drug abuse in the previous year.

Outcomes/endpoints

The co-primary endpoints were the proportion of patients with PASI 75 response and PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline, at Week 12. Other endpoints that were assessed included PASI 90 and 100 at different timepoints as well as patient-reported outcomes e.g. DLQI.

Randomisation/ Treatments

In **Part 1** patients were randomized on Day 1 (Week 0, Visit 2) in a 2:2:1 ratio to one of 3 treatment arms to receive Tildrakizumab 200 mg subcutaneously (SC) at Weeks 0 and 4 (Arm A), Tildrakizumab 100 mg SC at Weeks 0 and 4 (Arm B) or Tildrakizumab placebo SC at Weeks 0 and 4 (Arm C).
In **Part 2** patients initially randomized to placebo (Arm C) were re-randomized in a 1:1 ratio to receive either tildrakizumab 200 or 100 mg at Week 12 and 16. At Week 28, all patients were assessed for clinical response (PASI and PGA). Patients who did not achieve at least 50% improvement from baseline PASI (non-responders) were discontinued.
In **Part 3** responders (75% improvement from baseline PASI) were re-randomized in a 1:1 ratio to either continue on their initial treatment or to receive placebo every 4 weeks until relapse. Once relapse occurred the tildrakizumab dose that the patient was originally randomized to at baseline was re-initiated. Partial responders from Arm A remained on tildrakizumab 200 mg every 12 weeks, while these patients from Arm B were re-randomized in a 1:1 ratio to receive tildrakizumab 100 mg or tildrakizumab 200 mg every 12 weeks. Upon completion of Part 3, patients who were eligible may have entered the long-term safety extension study that will assess the long-term safety/tolerability of tildrakizumab.

Sample size

The sample size of study P10 was chosen to assure a substantial safety database. Approximately 750 patients (300 - tildrakizumab 200 mg, 300 – tildrakizumab, 150 - placebo) were to be included. Assuming a placebo rate of 10% for both PASI 75 response rate and proportion of patients with PGA "clear" or "minimal" with at least a 2 grade reduction from baseline, the trial had more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response rate and to detect a 55% difference in proportion of patients with PGA response, using a 2-sided chi-square test at alpha=0.05.

Assuming a placebo rate of 2% for PASI 90 response, the trial had more than 99% power to detect a 30% difference between tildrakizumab and placebo in PASI 90 response rate. Assuming a placebo rate of 1% for PASI 100 response, the trial had 99% power to detect a 10% difference between tildrakizumab and placebo in PASI 100 response rate.

Blinding (masking)

Tildrakizumab and its matching placebo were identical in appearance and were packaged identically to so that treatment blind was maintained. All patients underwent administration of additional placebo doses to maintain blinding.

Statistical methods

The primary efficacy analysis was based on the FAS of all randomized patients who received at least 1 dose of trial medication. The co-primary endpoints of PASI 75 response rate and the proportion of patients with PGA of “clear” or “minimal” with at least a 2 grade reduction from baseline at week 12 were analysed by means of a CMH test stratified by body weight and prior exposure to biologic therapy for psoriasis. Each dose of tildrakizumab was compared to placebo. Missing PASI 75 / PGA response information was imputed as non-response.

In order to assess the robustness of the primary analysis, supportive PP and an ITT analyses were performed using the same CMH test and missing data handling approach as described above. Other supportive analyses were conducted based on the FAS population, where missing data were imputed using the last observation carried forward (LOCF) approach and multiple imputation respectively. The imputation model was built for the underlying PASI score and PGA score respectively, including covariates such as age, gender, race, region, body mass index (BMI), psoriatic arthritis, prior exposure to biologics therapy, baseline PASI, baseline PGA, and baseline BSA.

In general dichotomous endpoints were analysed using the same CMH model as mentioned above for the co-primary endpoints. For the key secondary endpoints a non-responder imputation was applied to account for missing data otherwise missing data were treated as missing. Change in DLQI score from baseline at week 12; change in HAQ from baseline at week 12; and change in PGAP from baseline at week 12, were analysed using a constrained longitudinal data analysis (cLDA) method. The cLDA model assumed a common mean score across treatment groups at baseline and a different mean for each treatment at each post-baseline time point. In this model, the response vector consisted of the baseline measurement and the measurement observed at each post-baseline time point. Time was treated as a categorical variable. The analysis model adjusted for body weight, prior exposure to biologic therapy for psoriasis, time, and the interaction of treatment by time. An unstructured covariance matrix was used to model the correlation among repeated measurements.

Multiplicity for testing the co-primary and key secondary endpoints across the 2 tildrakizumab doses was controlled using a gate-keeping sequential testing procedure.

Results

Participant flow

The patients study disposition is presented below in the table below:

Table 7: Study disposition

	Placebo		MK-3222 100 mg		MK-3222 200 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	155		309		308		772[†]	
Study Disposition								
Completed	124	(80.0)	250	(80.9)	264	(85.7)	638	(82.6)
Discontinued	31	(20.0)	59	(19.1)	44	(14.3)	134	(17.4)
Adverse Events	1	(0.6)	3	(1.0)	10	(3.2)	14	(1.8)
Death	0		0		1	(0.3)	1	(0.1)
Lack of Efficacy	8	(5.2)	12	(3.9)	4	(1.3)	24	(3.1)
Lost to Follow-up	4	(2.6)	9	(2.9)	4	(1.3)	17	(2.2)
Non-Compliance with Study Drug	0		2	(0.6)	1	(0.3)	3	(0.4)
Physician Decision	2	(1.3)	6	(1.9)	1	(0.3)	9	(1.2)
Pregnancy	1	(0.6)	0		1	(0.3)	2	(0.3)
Progressive Disease	1	(0.6)	1	(0.3)	0		2	(0.3)
Protocol Violation	1	(0.6)	1	(0.3)	4	(1.3)	6	(0.8)
Study Terminated by Sponsor	0		0		0		0	
Withdrawal by Subjects	10	(6.5)	14	(4.5)	11	(3.6)	35	(4.5)
Other Protocol Specified Criteria	3	(1.9)	11	(3.6)	7	(2.3)	21	(2.7)
Long-Term Extension Study								
Entered Long-Term Extension Study	120	(77.4)	194	(62.8)	192	(62.3)	506	(65.5)
Did Not Enter Long-Term Extension Study	35	(22.6)	115	(37.2)	116	(37.7)	266	(34.5)
Follow-Up[‡]								
Entered Follow-up	13	(8.4)	62	(20.1)	71	(23.1)	146	(18.9)
Did Not Enter Follow-up	22	(14.2)	53	(17.2)	45	(14.6)	120	(15.5)

[†]Number of subjects randomized but never received study medication: 0 in MK-3222 200 mg, 0 in MK-3222 100 mg, and 1 in Placebo.
[‡]Does not include subjects who entered the extension study.

Conduct of the study

Amendments

The initial protocol, dated 14-JUN-2012, was amended 8 times. Amendment 1, 5 and 7 were global, while Amendment 2, 3, 4, 6 and 8 were applicable for sites in Japan only.

Protocol Amendment 1, dated 12-SEP-2012 (Global):

- Patients with PASI response <50% (non-responders) from all Arms at Week 28 were to be discontinued in order to maintain blind.
- Revision of Inclusion Criterion #9 (base study) and Inclusion Criterion #5 (long-term safety extension study) regarding contraception measures.
- Addition of Inclusion Criterion #14 (base study) for patients with psoriatic arthritis at baseline enrolled at Japanese sites: if patients were on NSAIDs, they should have been in a stable dose for at least 4 weeks prior to the first dose of study medication and were not anticipated to have an increase in the dose over the course of the trial.

Protocol Amendment 5 (010-05), dated 14-JAN-2014 (Global):

- Removal of Visit 35 in the follow-up period.

- The Wording regarding the follow-up visits was revised to state that patients who discontinued early from the base or long-term safety extension study were to continue with the visits in the follow-up period.

Protocol Amendment 7 (010-07), dated 08-JAN-2016 (Global):

- The PASI 100 response endpoint at Week 12 was upgraded to a key secondary endpoint. Statistical analysis related to this endpoint was revised to reflect the change.
- Addition of PASI 100 response rate as another secondary endpoint/objective in the long-term safety extension study.

Protocol Deviations

Major protocol deviations were reported at a greater incidence in the informed consent category (32.1% of patients) compared with all other deviation categories. Major protocol deviations related to informed consent included, but were not limited to, subject not signing the current version of the informed consent, wrong or missing date of signature on the informed consent, and lack of investigator involvement in the consent process. Protocol deviations that were considered to have the potential to affect results of the co-primary endpoints of the study (referred as protocol violations) were pre-specified as reasons for exclusion from the PP analysis.

Upon request from CHMP, the applicant provided further information on the above concerns regarding the outcome of the GCP inspections GCP/2017/017 and GCP/2017/034. The overall high number of protocol deviations revealed deficiencies in the process management of the study. However, further assessment and review, the impact on the protocol deviations was considered negligible.

Baseline data

The baseline data are presented in Table below.

Table 8:

	Placebo n (%)	MK-3222 100 mg n (%)	MK-3222 200 mg n (%)	Total n (%)
Subjects in population	155	309	308	772
Gender				
Male	100 (64.5)	207 (67.0)	226 (73.4)	533 (69.0)
Female	55 (35.5)	102 (33.0)	82 (26.6)	239 (31.0)
Age (years)				
<65	136 (87.7)	281 (90.9)	279 (90.6)	696 (90.2)
≥65	18 (11.6)	28 (9.1)	29 (9.4)	75 (9.7)
Mean	47.9	46.4	46.9	46.9
SD	13.55	13.09	13.16	13.21
Median	47.5	46.0	48.0	47.0
Range	19 to 76	18 to 82	18 to 76	18 to 82
Race				
American Indian or Alaska Native	1 (0.6)	0	0	1 (0.1)
Black	6 (3.9)	12 (3.9)	8 (2.6)	26 (3.4)
Native Hawaiian or Other Pacific Island	0	2 (0.6)	2 (0.6)	4 (0.5)
White	101 (65.2)	217 (70.2)	209 (67.9)	527 (68.3)
Asian	42 (27.1)	70 (22.7)	83 (26.9)	195 (25.3)
Multi-Racial	4 (2.6)	8 (2.6)	6 (1.9)	18 (2.3)
Missing	1 (0.6)	0	0	1 (0.1)
Hispanic or Latino	19 (12.3)	34 (11.0)	37 (12.0)	90 (11.7)
Not Hispanic or Latino	135 (87.1)	275 (89.0)	271 (88.0)	681 (88.2)
Not Reported	0	0	0	0
Unknown	1 (0.6)	0	0	1 (0.1)
Weight (kg)				
Subjects with data	154	309	308	771
Mean	87.50	88.53	88.87	88.46
SD	26.043	23.870	24.089	24.378
Median	84.50	86.00	85.75	85.70
Range	46.0 to 180.2	40.9 to 192.3	41.0 to 222.2	40.9 to 222.2
Height (cm)				
Subjects with data	154	308	308	770
Mean	169.51	170.66	171.04	170.58
SD	10.736	9.557	9.988	9.977
Median	170.10	171.00	172.60	171.60
Range	129.5 to 196.5	144.8 to 193.0	128.4 to 195.6	128.4 to 196.5
Psoriatic Arthritis				
Yes	19 (12.3)	54 (17.5)	60 (19.5)	133 (17.2)
No	136 (87.7)	255 (82.5)	248 (80.5)	639 (82.8)

Demographic and baseline characteristics were similar among the treatment groups. The majority was male (69%) and white (68.3%). However, the number of patients with psoriatic arthritis was higher in the 100 mg and tildrakizumab 200 mg groups (17.5% and 19.5%, respectively) compared to the placebo group (12.3%). The most common secondary diagnoses were Metabolism and Nutrition Disorders (31.9%), Musculoskeletal and Connective Tissue Disorders (31.5%), and Vascular Disorders (30.7%) and were generally similar across treatment groups. The most common prior medication was corticosteroids, dermatological preparations (54.9%) followed by immunosuppressants (36.5%).

Numbers analysed

772 patients were enrolled of which 638 completed the study. Of the 772 randomized patients, 27 (3.5%) were excluded from the PP analysis population due to protocol deviations, most frequently reported violation in the category of prohibited medication. The most common reason for discontinuation was withdrawal by the patients (4.5%), followed by lack of efficacy (3.1%).

Outcomes and estimation

- **PASI 75 Response at Week 12**

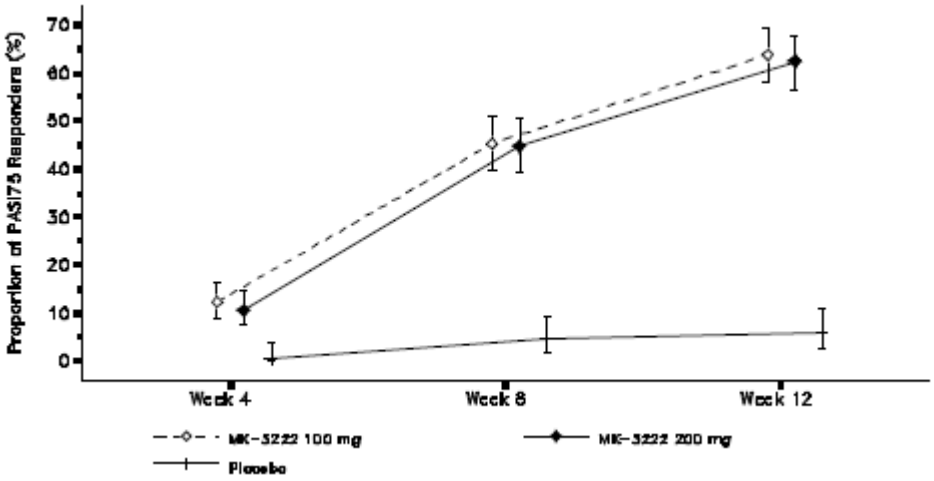
For the co-primary endpoint, the proportion of patients achieving a **PASI 75 response at Week 12** was significantly higher in the tildrakizumab 100 mg (63.8%) and tildrakizumab 200 mg (62.3%) groups compared with the placebo (5.8%) group (p<0.001 each).

Table 9: Proportion of Patients with PASI75 Response at Week 12

Statistics	Placebo N=154	MK-3222 100 mg N=309	MK-3222 200 mg N=308
PASI75 (Week 12)			
Subjects with data	154	309	308
Responders (%)[†]	9 (5.8)	197 (63.8)	192 (62.3)
Difference in % vs. Placebo (95% CI)[‡]		58.0 (51.0, 64.1)	56.6 (49.6, 62.8)
P-value[§]		<0.001	<0.001

[†]Percentages are based on subjects with data, which includes both observed and imputed data.
[‡]Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
[§]P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Figure 10: Proportion of Patients With PASI75 Response and 95% Confidence Interval Over Time (Missing=NR)(Full Analysis Set)



- **PGA Score of "Clear" or "Minimal" With at Least 2 Grade Reduction from Baseline at Week 12**

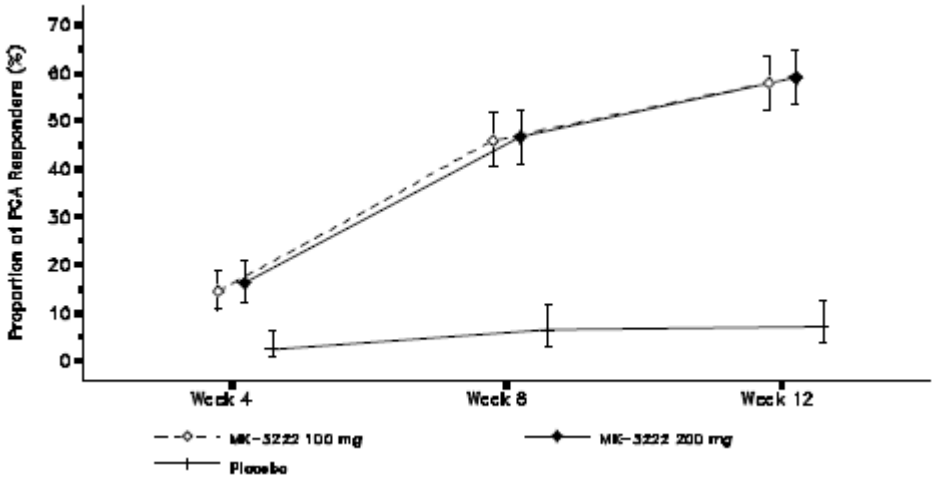
Regarding the second co-primary endpoint, the proportion of patients with a **PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline at Week 12** was significantly greater in the tildrakizumab 100 mg (57.9%) and tildrakizumab 200 mg (59.1%) groups compared with the placebo (7.1%) group (p<0.001 each).

Table 10: Proportion of Patients with PGA Score of Clear or Minimal, With at Least 2 Grade Reduction From Baseline at Week 12

Statistics	Placebo N=154	MK-3222 100 mg N=309	MK-3222 200 mg N=308
PGA (Week 12)			
Subjects with data	154	309	308
Responders (%)[†]	11 (7.1)	179 (57.9)	182 (59.1)
Difference in % vs. Placebo (95% CI)[‡]		50.9 (43.6, 57.4)	52.1 (44.8, 58.5)
P-value[§]		<0.001	<0.001

[†]Percentages are based on subjects with data, which includes both observed and imputed data.
[‡]Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
[§]P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PGA = Physician's Global Assessment.

Figure 11: Proportion of Patients with PGA Score of Clear or Minimal, With at Least 2 Grade Reduction From Baseline and 95% Confidence Interval



The key secondary endpoints **PASI 90** and **100 at week 12** as well as the other secondary endpoints support the efficacy shown for the co-primary endpoints.

Table 11: Proportion of Patients with PASI90 Response at Week 12 (Missing=NR)

Statistics	Placebo N=154	MK-3222 100 mg N=309	MK-3222 200 mg N=308
PASI90 (Week 12)			
Subjects with data	154	309	308
Responders (%)[†]	4 (2.6)	107 (34.6)	109 (35.4)
Difference in % vs. Placebo (95% CI)[‡]		32.1 (25.9, 38.0)	32.9 (26.8, 38.8)
P-value[§]		<0.001	<0.001

[†]Percentages are based on subjects with data, which includes both observed and imputed data.
[‡]Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
[§]P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Figure 12: Proportion of Patients with PASI90 Response over Time (Full Analysis Set) Part 1 and Part 2

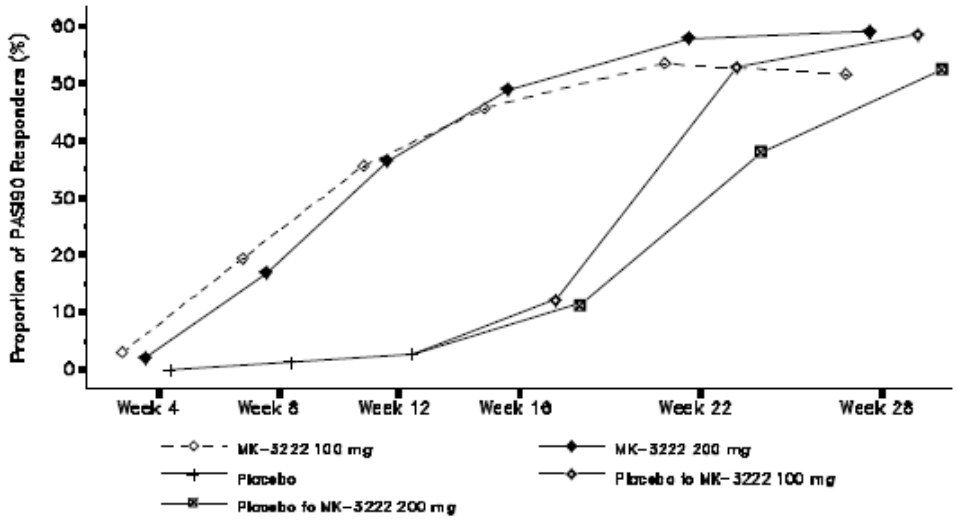


Table 12: Proportion of Patients with PASI100 Response at Week 12 (Missing=NR)

Statistics	Placebo N=154	MK-3222 100 mg N=309	MK-3222 200 mg N=308
PASI100 (Week 12)			
Subjects with data	154	309	308
Responders (%)[†]	2 (1.3)	43 (13.9)	43 (14.0)
Difference in % vs. Placebo (95% CI)[‡]		12.7 (8.0, 17.3)	12.7 (8.3, 17.2)
P-value[§]		<0.001	<0.001

[†]Percentages are based on subjects with data, which includes both observed and imputed data.
[‡]Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
[§]P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Figure 13: Proportion of Patients with PASI100 Response over Time (Full Analysis Set) Part 1 and Part 2

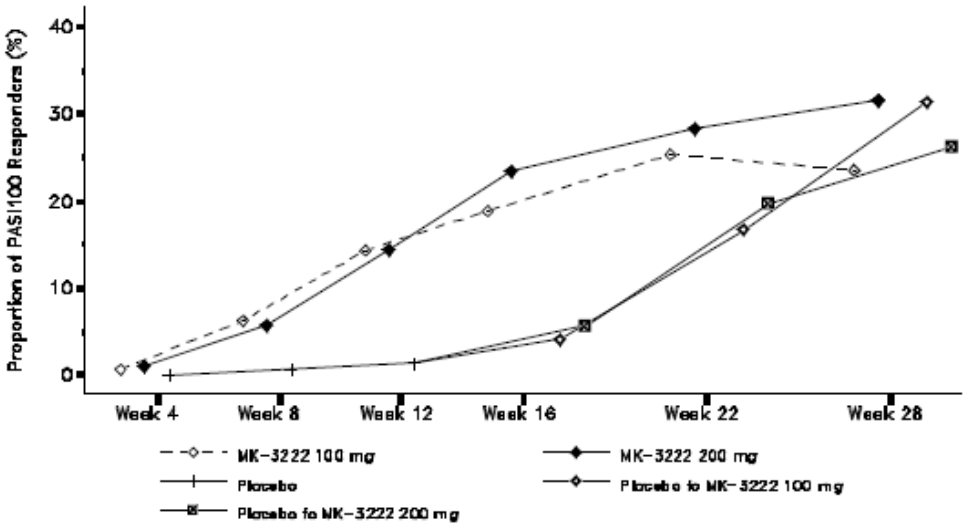
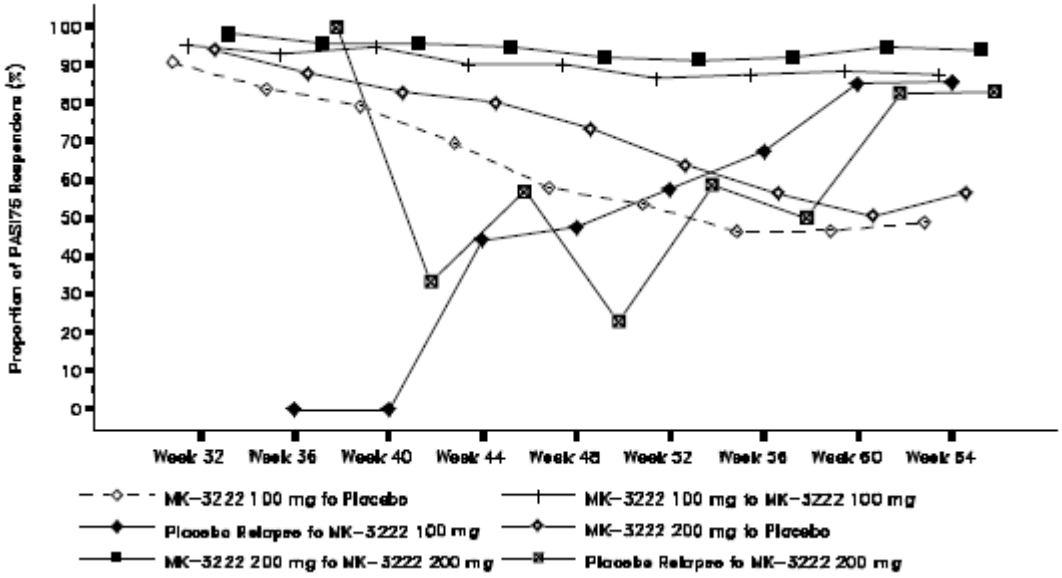


Figure 14: PASI 75 Response Over Time: Part 3 (Full Analysis Set) Patients Randomized to MK-3222 100 mg or MK-3222 200 mg in Part 1 Who Were PASI75 Responders at Week 28



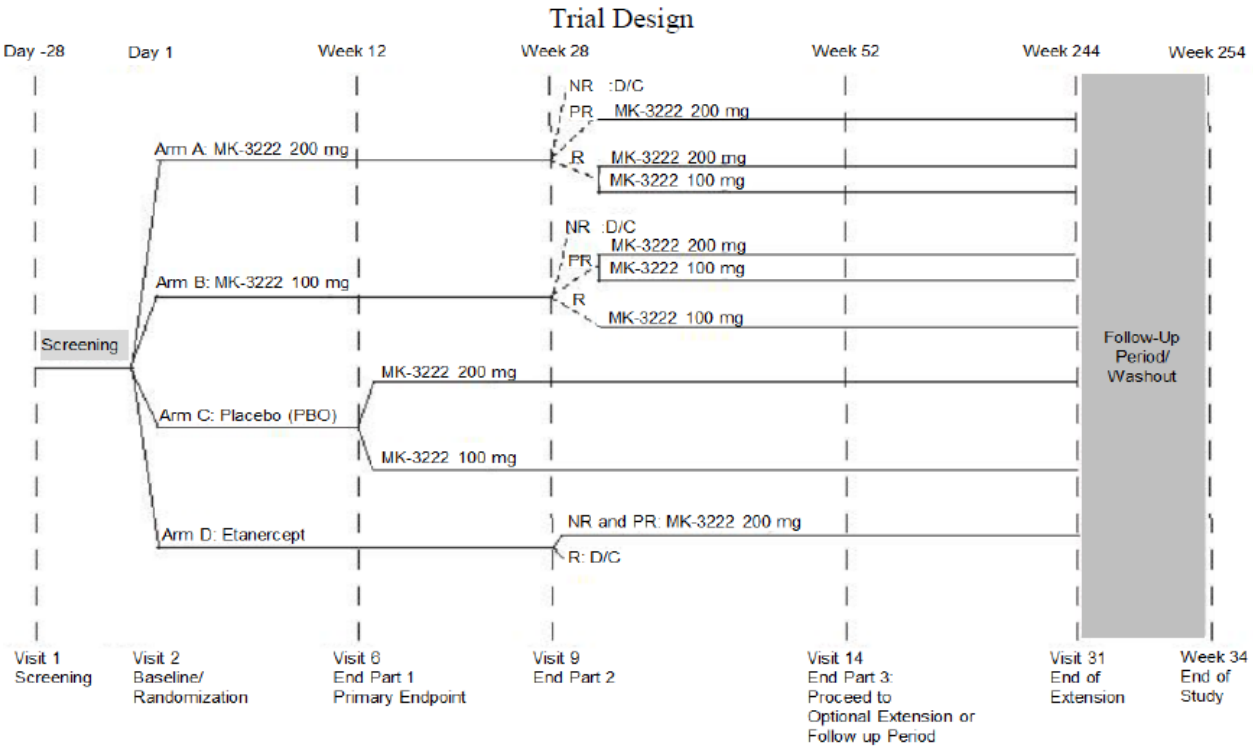
Subgroup analyses were performed with regards to Body weight, prior exposure to biologic treatment, failure to prior systemic treatment, age, gender, race, region, history of TNF antagonist response and psoriatic arthritis. Overall, results were consistent across the various subgroups and were similar to those seen in the FAS population.

2.5.2.2. Study P011 (reSURFACE2)

Study objectives

Study P011 was a Phase 3, randomized, double-blind, active-comparator and placebo-controlled, parallel-group trial to evaluate the efficacy and safety/tolerability of subcutaneous (SC) tildrakizumab, followed by an optional long-term safety extension study, in patients with moderate-to-severe chronic plaque psoriasis.

Figure 15: Methods / study design



SCREENING/ WASHOUT	BASE STUDY TREATMENT PERIOD			LONG-TERM SAFETY EXTENSION (OPTIONAL) 4 YEARS	FOLLOW-UP PERIOD 20 WEEKS
	PART 1 12 WEEKS	PART 2 16 WEEKS	PART 3 24 WEEKS		

Non-responders (NR) were subjects who achieved <50% improvement in PASI response from baseline.
At Week 28, non responders from Arms A and B were discontinued.
Partial responders (PR) were subjects who achieved ≥50% but <75% improvement in PASI response from baseline.
Responders (R) were subjects who achieved ≥75% improvement in PASI response from baseline.
D/C = discontinuation; PASI = Psoriasis Area and Severity Index.

Study participants

The eligibility criteria were similar to study P010.

Endpoints / outcomes

The primary objective of study P011 was to assess the efficacy of tildrakizumab compared to placebo with regards to PASI 75 and PGA score of “clear” or “minimal” with at least a 2 grade reduction from baseline at Week 12. One of the key secondary endpoint was to assess the efficacy of tildrakizumab compared to etanercept.

The co-primary endpoints were proportions of patients with PASI 75 response and PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12. The secondary endpoints included PASI 75, 90, 100 and PGA at different time points as well as patient reported outcomes e.g. DLQI at different timepoints.

Randomisation

Approximately 1050 subjects were to be randomized at approximately 120 sites. The duration of the base study was up to 76 weeks for each subject. This included a 4-week screening period, a 12-week Part 1 period, a 16-week Part 2 period, and a 24-week Part 3 period. Subjects who completed Part 3 of the trial were eligible to participate in a long-term safety extension study to evaluate the long-term safety and maintenance of effect of tildrakizumab.

In **Part 1** patients were randomized on Day 1 (Week 0, Visit 2) in a 2:2:1:2 ratio using to receive tildrakizumab 200 mg SC at Weeks 0 and 4 and etanercept placebo SC twice weekly (Arm A), tildrakizumab 100 mg SC at Weeks 0 and 4 and etanercept placebo SC twice weekly (Arm B), tildrakizumab placebo SC at Weeks 0 and 4 and etanercept placebo SC twice weekly (Arm C) or tildrakizumab placebo at Weeks 0 and 4 and etanercept 50 mg SC twice weekly (Arm D). Randomization was conducted by region and stratified by Body weight (≤90 kg or >90 kg), failure to respond to at least one traditional systemic medication and prior exposure to biologics therapy for psoriasis. At Week 12, patients were assessed for clinical response

In **Part 2** patients originally randomized to tildrakizumab (Arms A and B) continued on their current treatment and received an additional dose of study medication at Week 16. At Week 12, all patients initially randomized to placebo (Arm C) were re-randomized to receive tildrakizumab 100 mg or tildrakizumab 200 mg at week 12 and received additional doses of study medication according to their re-randomized treatment assignment at Weeks 16 and 28. All patients randomized to etanercept (Arm D) received once-weekly doses of etanercept until Week 28. At Week 28, all patients were assessed for clinical response.

In **Part 3** responders (75% improvement in PASI score from baseline) in Arm A at Week 28 were re-randomized in a 1:1 ratio to tildrakizumab 200 mg or tildrakizumab 100 mg, administered at Weeks 28, 40, and 52. Patients, who achieved partial response (≥ 50% but < 75% improvement in PASI score from baseline) at Week 28, continued to receive tildrakizumab 200 mg every 12 weeks. Non-responders (<50% improvement in PASI) were discontinued.

Responders in Arm B who received tildrakizumab 100 mg in Part 1 and Part 2, continued to receive tildrakizumab 100 mg every 12 weeks. Partial responders were re-randomized in a 1:1 ratio to tildrakizumab 100 mg or tildrakizumab 200 mg every 12 weeks. Non-responders were discontinued from the study.

Patients in Arm C continued receiving tildrakizumab according to their re-randomized treatment assignment during Part 2.

Partial responders and non-responders, who received etanercept (Arm D) in Part 1 and Part 2, were assigned to receive tildrakizumab 200 mg at Weeks 32, 36, and 48. Responders in the etanercept arm were discontinued from the study at week 28. Patients, who completed the base study and achieved at least 50% improvement in PASI from baseline at the end of Part 3 and satisfied all other entry criteria, were eligible to participate in the long-term safety extension. The 192-week long-term safety extension study is currently ongoing.

Sample size

Approximately 1050 subjects in total were planned to receive 2:2:1:2 randomized treatment assignment to: (A) tildrakizumab 200 mg (N=300), (B) tildrakizumab 100 mg (N=300), (C) placebo (N=150), or (D) etanercept (N=300).

With this sample size, assuming a placebo rate of 10% for both PASI 75 response and PGA “clear” or “minimal” with at least a 2 grade reduction from baseline, the trial had more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response and to detect a 55% difference in PGA “clear” or “minimal” with at least a 2 grade reduction from baseline.

In addition, a difference of 17% between a tildrakizumab dose and etanercept for PASI 75 response rate could be detected with more than 98% power assuming an etanercept rate of approximately 56%; and a difference of 20% between a tildrakizumab dose and etanercept for PGA “clear” or “minimal” with at least a 2 grade reduction from baseline could be detected with more than 99% power assuming an etanercept rate of approximately 49%, using 2-sided test at significance level of alpha=0.05

Assuming a placebo rate of 2% for PASI 90 response, the trial had more than 99% power to detect a 30% difference between tildrakizumab and placebo in PASI 90 response rate.

Assuming a placebo rate of 1% for PASI 100 response, the trial had 99% power to detect a 10% difference between tildrakizumab and placebo in PASI 100 response rate.

A difference of 10% between a tildrakizumab dose and etanercept for PASI 90 response rate could be detected with 73% power assuming an etanercept rate of approximately 30%.

A difference of 5% between a tildrakizumab dose and etanercept for PASI 100 response rate could be detected with 46% power assuming an etanercept rate of approximately 10%.

Assuming a screen failure rate of 15%, approximately 1235 subjects were to be screened.

Blinding (masking)

All subjects were administered study medication or matching placebo for both tildrakizumab and etanercept according to their treatment assignments.

Statistical methods

Statistical Methods for Efficacy Analysis Co-Primary Efficacy Endpoints

The co-primary endpoints of PASI 75 response rate and the proportion of subjects with PGA of "clear" or "minimal" with at least a 2 grade reduction from baseline at Week 12 were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (Yes, No). Each dose of tildrakizumab was compared to placebo. Subjects with missing data were treated as non-responders.

The study was declared positive if tildrakizumab 200 mg was superior to placebo on both co-primary endpoints based on the FAS analysis.

Supportive Analyses for the Co-Primary Efficacy Endpoints

A PP analysis and an ITT analysis was performed as supportive analyses using the same CMH test and missing data handling approach as described above. A second supportive analysis was conducted based on the FAS population, where missing data were imputed using the last observation carried forward (LOCF) approach.

An additional sensitivity analysis was conducted using multiple imputation. Specifically, an imputation model was built for the underlying PASI score and PGA score respectively, including comprehensive demographic variables and baseline disease characteristics as covariates such as age, gender, race, region, body mass index (BMI), psoriatic arthritis, prior exposure to biologics therapy, baseline PASI, baseline PGA, and baseline BSA. The dichotomized PASI 75 response and PGA response (i.e., PGA score of "clear" or "minimal") based on the multiple imputed PASI score and PGA score was analyzed.

Key Secondary Efficacy Endpoints

The key secondary endpoints were analyzed in the same fashion as the primary endpoints with comparisons to placebo and etanercept.

Other Secondary Efficacy Endpoints – Part 3 (Week 28 to Week 52)

Responder Analysis

Subjects who were originally randomized to tildrakizumab 200 mg (Arm A) and who were PASI 75 responders at Week 28 were re-randomized to either remain on the original dose regimen or to receive dose down-titration of tildrakizumab 100 mg starting from Week 28.

The PASI 75 response rate and the proportion of subjects with PGA of “clear” or “minimal” with at least a 2 grade reduction from baseline at Week 52 and over time were evaluated for these subjects comparing those who received lower dose of 100 mg with those who remained on 200 mg. Additionally, the change and percent change from baseline in PASI score were summarized over time for the treatment group comparison described above.

Partial Responder Analysis

Subjects who were originally randomized to tildrakizumab 100 mg (Arm B) and who were partial responders at Week 28 were re-randomized to either remain on the original dose regimen or to receive dose up-titration of tildrakizumab 200 mg starting from Week 28. The PASI 75 response rate and the proportion of subjects with PGA of “clear” or “minimal” with at least a 2 grade reduction from baseline at Week 52 and over time were evaluated for these subjects comparing those who received higher dose of 200 mg with those who remained on 100 mg. Additionally, the change and percent change from baseline in PASI score were summarized over time for the treatment group comparison described earlier.

Results

Participant flow

756 of initially 1090 patients completed the trial. The most common reason for discontinuation was in the category of Other Protocol Specified Criteria. The rate of discontinuation for other protocol specified criteria was numerically lower in the placebo group (1.9%) compared with the tildrakizumab 100 mg and 200 mg groups and the etanercept group (10.7%, 5.4%, and 51.1%, respectively) because placebo-treated subjects were not discontinued while etanercept responders and tildrakizumab 100 mg and 200 mg non-responders were discontinued based on their responder status at Week 28.

Other reasons for discontinuation of study medication were generally similar between the 4 treatment groups. Of the 1090 randomized subjects, 1026 (94.1%) subjects completed Part 1 of the base study (the initial 12-week treatment period); 1025 subjects continued into Part 2 of the base study.

Of these subjects, 995 (97.1%) subjects completed Part 2 (i.e., a total of 28 weeks of treatment); 794 subjects continued into Part 3 of the base study. Of these subjects, 756 (95.2%) subjects completed Part 3 (24-week treatment period).

Subjects who completed the base study were eligible to participate in the optional long-term safety extension study provided they met the extension eligibility criteria. Of the 756 (69.4%) subjects who completed the base study, 731 (67.1%) subjects entered the long-term safety extension study. All subjects who were discontinued from the base study or completed the base study but did not enter the long-term safety extension study were to enter a 20-week follow-up/washout period to monitor

safety/tolerability, PK, and ADA response.

Of the 359 (32.9%) subjects who did not enter the long-term safety extension study, 196 (18%) subjects entered the follow-up period and 163 (15%) subjects did not enter the follow-up period.

Table 13: Disposition of Subjects (All Subjects Randomized) Base Study

	Placebo		MK-3222 100 mg		MK-3222 200 mg		Etanercept		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	156		307		314		313		1090[†]	
Study Disposition										
Completed	131	(84.0)	241	(78.5)	270	(86.0)	114	(36.4)	756	(69.4)
Discontinued	25	(16.0)	66	(21.5)	44	(14.0)	199	(63.6)	334	(30.6)
Adverse Events	3	(1.9)	6	(2.0)	5	(1.6)	10	(3.2)	24	(2.2)
Death[§]	0		3	(1.0)	0		0		3	(0.3)
Lack of Efficacy	4	(2.6)	2	(0.7)	1	(0.3)	6	(1.9)	13	(1.2)
Lost to Follow-up	5	(3.2)	7	(2.3)	4	(1.3)	5	(1.6)	21	(1.9)
Non-Compliance with Study Drug	0		0		1	(0.3)	1	(0.3)	2	(0.2)
Physician Decision	0		0		1	(0.3)	4	(1.3)	5	(0.5)
Pregnancy	0		2	(0.7)	0		2	(0.6)	4	(0.4)
Progressive Disease	0		0		0		1	(0.3)	1	(0.1)
Protocol Violation	1	(0.6)	1	(0.3)	2	(0.6)	0		4	(0.4)
Study Terminated by Sponsor	0		0		0		0		0	
Withdrawal by Subjects	9	(5.8)	12	(3.9)	13	(4.1)	10	(3.2)	44	(4.0)
Other Protocol Specified Criteria	3	(1.9)	33	(10.7)	17	(5.4)	160	(51.1)	213	(19.5)

Conduct of the study

The most common major deviations were regarding informed consent (326 deviations [29.9% of total deviations]), investigational product administration or study treatment (240 deviations [22.0% of total deviations]), and procedures or tests (212 deviations [19.4% of total deviations]).

The PP population excluded subjects from the FAS population due to important deviations that could have affected results of the co-primary endpoints. A total of 175 subjects were excluded from the PP analysis population in Part 1 (N=140) or Part 2 (N=167) of the base study. The most common reason subjects were excluded from the PP population was due to not meeting the PASI, PGA, or BSA inclusion criteria.

Baseline characteristics

Demographic characteristics were generally similar between the 4 treatment groups. The majority of patients were male and white. 91.1 % were less than 65 years of age. The mean weight was 88.58 kg with a range from 44 to 194.7 kg. 14.1% had a diagnosis of Psoriatic Arthritis. The most common secondary diagnoses were Vascular Disorders (27.5%), Metabolism and Nutrition Disorders (26%), and Musculoskeletal and Connective Tissue Disorders (25.5%) and were generally similar across treatment groups.

Table 14 Baseline characteristics

	Placebo n (%)	MK-3222 100 mg n (%)	MK-3222 200 mg n (%)	Etanercept n (%)	Total n (%)
Subjects in population	156	307	314	313	1090
Gender					
Male	112 (71.8)	220 (71.7)	225 (71.7)	222 (70.9)	779 (71.5)
Female	44 (28.2)	87 (28.3)	89 (28.3)	91 (29.1)	311 (28.5)
Age (years)					
<65	142 (91.0)	280 (91.2)	289 (92.0)	282 (90.1)	993 (91.1)
≥65	14 (9.0)	27 (8.8)	25 (8.0)	31 (9.9)	97 (8.9)
Mean	46.4	44.6	44.6	45.8	45.2
SD	12.20	13.59	13.62	13.97	13.52
Median	46.0	44.0	45.0	48.0	45.5
Range	20 to 76	19 to 80	19 to 80	19 to 81	19 to 81
Race					
American Indian or Alaska Native	0	1 (0.3)	0	1 (0.3)	2 (0.2)
Black	1 (0.6)	7 (2.3)	8 (2.5)	8 (2.6)	24 (2.2)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	0	0	1 (0.1)
White	144 (92.3)	279 (90.9)	284 (90.4)	289 (92.3)	996 (91.4)
Asian	3 (1.9)	9 (2.9)	14 (4.5)	10 (3.2)	36 (3.3)
Multi-Racial	3 (1.9)	7 (2.3)	2 (0.6)	3 (1.0)	15 (1.4)
Missing	4 (2.6)	4 (1.3)	6 (1.9)	2 (0.6)	16 (1.5)

	Placebo n (%)	MK-3222 100 mg n (%)	MK-3222 200 mg n (%)	Etanercept n (%)	Total n (%)
Ethnicity[†]					
Hispanic or Latino	16 (10.3)	24 (7.8)	23 (7.3)	23 (7.3)	86 (7.9)
Not Hispanic or Latino	135 (86.5)	273 (88.9)	282 (89.8)	281 (89.8)	971 (89.1)
Not Reported	1 (0.6)	3 (1.0)	3 (1.0)	5 (1.6)	12 (1.1)
Unknown	1 (0.6)	4 (1.3)	3 (1.0)	2 (0.6)	10 (0.9)
Weight (kg)					
Subjects with data	156	307	314	313	1090
Mean	88.74	89.35	88.35	87.97	88.58
SD	22.727	22.122	21.231	21.480	21.750
Median	86.45	87.50	86.00	85.70	86.35
Range	44.0 to 166.0	49.5 to 194.7	51.3 to 165.0	46.3 to 160.0	44.0 to 194.7
Height (cm)					
Subjects with data	156	306	314	313	1089
Mean	172.32	173.47	174.09	174.34	173.73
SD	9.759	9.667	10.614	9.833	10.018
Median	173.00	174.00	174.00	174.00	174.00
Range	148.5 to 196.0	148.1 to 198.0	117.5 to 197.0	148.0 to 211.0	117.5 to 211.0
Psoriatic Arthritis					
Yes	23 (14.7)	48 (15.6)	42 (13.4)	41 (13.1)	154 (14.1)
No	133 (85.3)	259 (84.4)	272 (86.6)	272 (86.9)	936 (85.9)

	Placebo n (%)	MK-3222 100 mg n (%)	MK-3222 200 mg n (%)	Etanercept n (%)	Total n (%)
Body Surface Area(%)					
Subjects with data	155	307	309	310	1081
Mean	31.3	34.2	31.8	31.6	32.4
SD	14.75	18.44	17.16	16.58	17.07
Median	29.0	30.0	28.0	28.0	29.0
Range	10 to 84	10 to 96	10 to 88	5 to 89	5 to 96

† Not reported: if ethnicity is not provided or available, Unknown: if ethnicity is not known, not observed, not recorded or refused.
SD = Standard deviation

Outcomes / endpoints

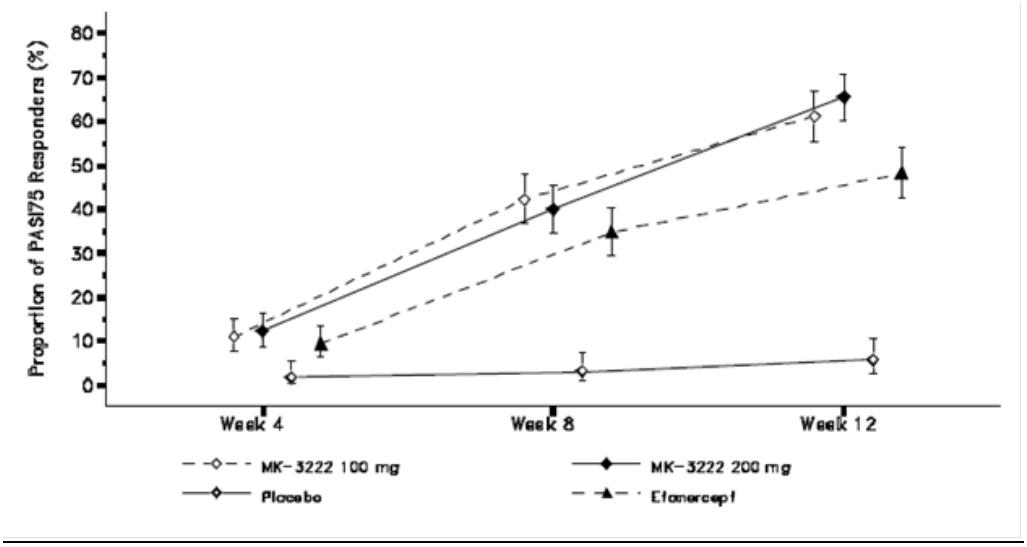
The proportion of patients achieving a **PASI 75 response at Week 12** was significantly greater in the tildrakizumab 100 mg (61.2%) and tildrakizumab 200 mg (65.6%) groups compared with the placebo (5.8%) and the etanercept (48.2%) group (p<0.001 each).

Table 15: Proportion of Patients with PASI75 Response at Week 12

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PASI75 (Week 12)				
Subjects with data	156	307	314	313
Responders (%)†	9 (5.8)	188 (61.2)	206 (65.6)	151 (48.2)
Difference in % vs. Placebo (95% CI)‡		55.5 (48.3, 61.8)	59.8 (52.9, 65.9)	
p-Value§		<0.001	<0.001	

† Percentages are based on subjects with data, which includes both observed and imputed data.
‡ Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
§ P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Figure 16: Proportion of Patients With PASI75 Response and 95% Confidence Interval Over Time (Missing=NR)(Full Analysis Set)



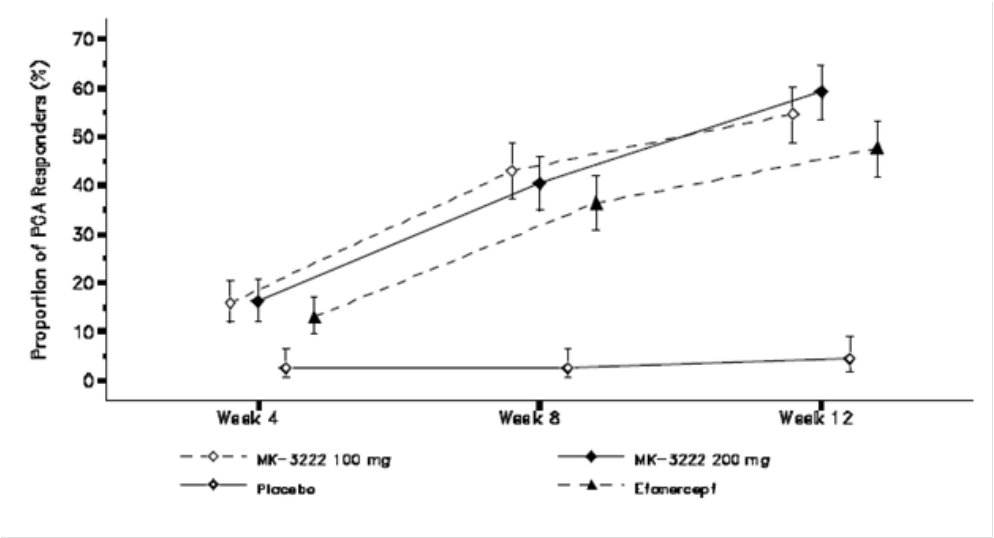
Regarding the second co-primary endpoint, the proportion of patients with a **PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline at Week 12** was significantly greater in the tildrakizumab 100 mg (54.7%) and tildrakizumab 200 mg (59.2%) groups compared with the placebo (4.5%) and etanercept (47.6%) group (p<0.001 each).

Table 16: Proportion of Patients with PGA Score of Clear or Minimal, With at Least 2 Grade Reduction From Baseline at Week 12 (Missing=NR)

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PGA (Week 12)				
Subjects with data	156	307	314	313
Responders (%)[†]	7 (4.5)	168 (54.7)	186 (59.2)	149 (47.6)
Difference in % vs. Placebo (95% CI)[‡]		50.2 (43.2, 56.5)	54.7 (47.9, 60.8)	
p-Value[§]		<0.001	<0.001	

[†] Percentages are based on subjects with data, which includes both observed and imputed data.
[‡] Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
[§] P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PGA = Physician's Global Assessment.

Figure 17: Proportion of Patients with PGA Score of Clear or Minimal, With At Least 2 Grade Reduction From Baseline (Missing=NR) and 95% Confidence Interval



The key secondary endpoints **PASI 90** and **100 at Week 12** as well as the other secondary endpoints support the efficacy shown for the co-primary endpoints.

Table 17: Proportion of Patients with PASI90 Response at Week 12 (Missing=NR)

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PASI90 (Week 12)				
Subjects with data	156	307	314	313
Responders (%)†	2 (1.3)	119 (38.8)	115 (36.6)	67 (21.4)
Difference in % vs. Placebo (95% CI)‡		37.5 (31.1, 43.4)	35.3 (29.2, 41.1)	
p-Value§		<0.001	<0.001	

† Percentages are based on subjects with data, which includes both observed and imputed data.
‡ Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
§ P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Table 18: Proportion of Patients with PASI100 Response at Week 12 (Missing=NR)

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PASI100 (Week 12)				
Subjects with data	156	307	314	313
Responders (%)†	0	38 (12.4)	37 (11.8)	15 (4.8)
Difference in % vs. Placebo (95% CI)‡		12.4 (8.5, 16.6)	11.7 (7.8, 16.0)	
p-Value§		<0.001	<0.001	

† Percentages are based on subjects with data, which includes both observed and imputed data.
‡ Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
§ P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Table 19: Proportion of patients With PASI75 Response at Week 28 (Missing=NR)

Statistics	MK-3222 100 mg N=294	MK-3222 200 mg N=299	Etanercept N=289
PASI75 (Week 28)			
Subjects with data	294	299	289
Responders (%)†	216 (73.5)	217 (72.6)	155 (53.6)
Difference in % vs. Etanercept (95% CI)‡	20.1 (12.4, 27.6)	19.2 (11.5, 26.7)	
p-Value§	<0.001	<0.001	

† Percentages are based on subjects with data, which includes both observed and imputed data.
‡ Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
§ P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 28 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 2.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.

Table 20: Proportion of Patients with PGA Score of Clear or Minimal, With at Least 2 Grade Reduction from Baseline at Week 12 - Comparison to Etanercept (Missing=NR)

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PGA (Week 12)				
Subjects with data	156	307	314	313
Responders (%)†	7 (4.5)	168 (54.7)	186 (59.2)	149 (47.6)
Difference in % vs. Etanercept (95% CI)‡		7.3 (-0.5, 15.0)	11.7 (4.0, 19.3)	
p-Value§		0.066	0.003	

† Percentages are based on subjects with data, which includes both observed and imputed data.
‡ Difference and CIs are calculated using Miettinen-Nurminen stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights.
§ P-values are calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (<=90kg, >90kg) and prior exposure to biologic therapy for psoriasis (yes/no). P-values are not adjusted for multiplicity.
NR = Non-responder; subjects with missing data at Week 0 or Week 12 are treated as non-responders.
N = Number of randomized subjects who received at least one dose of study medication in Part 1.
CI = Confidence interval; PGA = Physician's Global Assessment.

The secondary endpoint PGA Score of “Clear” or “Minimal” with at Least a 2 Grade Reduction from Baseline at Week 12: Tildrakizumab versus Etanercept presented a p-value of 0.066 which is

statistically not significant according to the pre-specified testing procedure. In the sequence of multiple testing procedure, the results of the following endpoints occurred after the failed test of the PGA score of tildrakizumab 100 mg compared to etanercept at Week 12. Hence, after adjusting for multiplicity using a gate-keeping sequential testing procedure, these results were not statistically significant.

The results of supportive analysis at Week 12 in the ITT population, PP population, FAS population using LOCF and in the FAS population using multiple imputations supported the conclusion from the primary analysis.

Ancillary analyses

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of efficacy for trial P010

Title: A 64-Week, Phase 3, Randomized, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Patients With Moderate-to-Severe Chronic Plaque Psoriasis			
Study identifier	P10		
Design	randomized, double-blind, placebo-controlled, parallel-group, multi-center study followed by an optional long-term safety extension study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		64 weeks N/A 192 weeks
Hypothesis	Superiority		
Treatment groups (part 1)	MK-3222 200 mg		2 tildrakizumab 100 mg/mL pre-filled syringes (PFS) subcutaneously (SC) at Weeks 0 and 4 N=308
	MK-3222 100 mg		1 tildrakizumab 100 mg/mL PFS SC and 1 placebo PFS SC at Weeks 0 and 4 N=309
	Placebo		2 placebo PFS SC at Weeks 0 and 4 N=155
Endpoints and definitions	Primary	PASI 75	Proportion of patients with PASI 75 response at Week 12
		PGA	Proportion of patients with a PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline at Week 12
	Key secondary	PASI 90	Proportion of patients with PASI 90 response at Week 12
		PASI 100	Proportion of patients with PASI 100 response at Week 12
Database lock	10-05-2016		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	FAS consisting of all randomized patients who received at least1 dose of part 1 study treatment			
Descriptive statistics and estimate variability	Treatment group	Placebo	**MK-3222 100 mg**	**MK-3222 200 mg**
	Number of patients	154	309	308
	PASI 75	9 (5.8%)	197 (63.8%)	192 (62.3%)
	95%-CI	2.7 – 10.8%	58.1 – 69.1%	56.7 – 67.8%
	PGA	11 (7.1%)	179 (57.9%)	182 (59.1%)
	95%-CI	3.6 – 12.4%	52.2 – 63.5%	53.4 – 64.6%
Effect estimate per comparison	PASI 75	Comparison groups	MK-3222 100 mg vs placebo	MK-3222 200 mg vs. placebo
		Difference	58.0%	56.6%
		95%-CI	51.0-64.1%	49.6-62.8%
		P-value	< 0.001	< 0.001
	PGA	Difference	50.9%	52.1%
		95%-CI	43.6-57.4%	44.8-58.5%
		P-value	< 0.001	< 0.001
Notes	With regard to the co-primary endpoints, both MK-3222 dosages are statistically significant superior to placebo.			
Analysis description	**Key Secondary Analyses**			
Analysis population and time point description	FAS consisting of all randomized patients who received at least1 dose of part 1 study treatment			
Descriptive statistics and estimate variability	Treatment group	Placebo	**MK-3222 100 mg**	**MK-3222 200 mg**
	Number of patients	154	309	308
	PASI 90	4 (2.6%)	107 (34.6%)	109 (35.4%)
	95%-CI	0.7 – 6.5%	29.3 – 40.2%	30.1 – 41.0%
	PASI 100	2 (1.3%)	43 (13.9%)	43 (14.0%)
	95%-CI	0.2 – 4.6%	10.3 – 18.3%	10.3 – 18.3%
Effect estimate per comparison	PASI 90	Comparison groups	MK-3222 100 mg vs placebo	MK-3222 200 mg vs. placebo
		Difference	32.1%	32.9%
		95%-CI	25.9-38.0%	26.8-38.8%
		P-value	< 0.001	< 0.001
	PASI 100	Difference	12.7%	12.7%
		95%-CI	8.0-17.3%	8.3-17.2%
		P-value	< 0.001	< 0.001

Notes	With regard to the key secondary endpoints, both MK-3222 dosages are statistically significant superior to placebo.

Table 22: Summary of efficacy for trial P011

Title: A 52-Week, Phase 3, Randomized, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Patients With Moderate-to–Severe Chronic Plaque Psoriasis					
Study identifier					
Design	randomized, double-blind, active-comparator and placebo-controlled, parallel-group, multi-center study followed by an optional long-term safety extension study				
	Duration of main phase:		52 weeks		
	Duration of Run-in phase:		N/A		
	Duration of Extension phase:		192 weeks		
Hypothesis	Superiority				
Treatment groups (part 1)	MK-3222 200 mg		Tildrakizumab 200 mg SC at Weeks 0 and 4 and etanercept placebo SC twice weekly N=314		
	MK-3222 100 mg		Tildrakizumab 100 mg SC at Weeks 0 and 4 and etanercept placebo SC twice weekly N=307		
	Placebo		Tildrakizumab placebo SC at Weeks 0 and 4 and etanercept placebo SC twice weekly N=156		
	Etanercept 50 mg		Etanercept 50 mg SC twice weekly and tildrakizumab placebo SC at weeks 0 and 4 N=313		
Endpoints and definitions	Primary	PASI 75	Proportion of patients with PASI 75 response at Week 12		
		PGA	Proportion of patients with a PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline at Week 12		
	Key secondary	PASI 90	Proportion of patients with PASI 90 response at Week 12		
		PASI 75/28	Proportion of patients with PASI 75 response at Week 12 and week 28		
		PGA /28	Proportion of patients with a PGA score of "clear" or "minimal", with at least a 2 grade reduction from baseline at Week 12 and week 28		
		PASI 100	Proportion of patients with PASI 100 response at Week 12		
Database lock	08-04-2016				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS consisting of all randomized patients who received at least1 dose of part 1 study treatment				
Descriptive statistics and estimate variability	Treatment group	Placebo	**MK-3222 100 mg**	**MK-3222 200 mg**	Etanercept
	Number of patients	156	307	314	313

	PASI 75	9 (5.8%)	188 (61.2%)	206 (65.6%)	151 (48.2%)
	95%-CI	2.7-10.7%	55.5–66.7%	60.1-70.9%	42.6-53.9%
	PGA	7 (4.5%)	168 (54.7%)	186 (59.2%)	149 (47.6%)
	95%-CI	1.8-9.0%	44.0-60.4%	53.6-64.7%	42.0-53.3%

Effect estimate per comparison	PASI 75	Comparison groups	MK-3222 100 mg vs placebo	MK-3222 200 mg vs. placebo
		Difference	55.5%	59.8%
		95%-CI	48.3 - 61.8%	52.9 - 65.9%
		P-value	< 0.001	< 0.001
	PGA	Difference	50.2%	54.7%
		95%-CI	43.2 - 56.5%	47.9 - 60.8%
		P-value	< 0.001	< 0.001
Notes	With regard to the co-primary endpoints, both MK-3222 dosages are significantly superior to placebo.			
Analysis description	**Secondary Analyses**			
Analysis population and time point description	FAS consisting of all randomized patients who received at least 1 dose of part 1 study treatment			

Descriptive statistics and estimate variability	Treatment group	Placebo	**MK-3222 100 mg**	**MK-3222 200 mg**	Etanercept
	Number of patients	156	307	314	313
	PASI 90	2 (1.3%)	119 (38.8%)	115 (36.6%)	67 (21.4%)
	95%-CI	0.2-4.6%	33.3-44.5%	31.3-42.2%	17.0-26.4%
	PASI 100	0	38(12.4%)	37 (11.8%)	15 (4.8%)
	95%-CI	0.0-2.3%	8.9-16.6%	8.4-15.9%	2.7-7.8%
	Number of patients		294	299	289
	PASI 75/28		216 (73.5%)	217 (72.6%)	155 (53.6%)
	95%-CI		68.0-78.4%	67.1-77.6%	47.7-59.5%
	PGA / 28		190 (64.6%)	207 (69.2%)	131 (45.3%)
	95%-CI		58.9-70.1%	63.7-74.4%	39.5-51.3%

Effect estimate per comparison	PASI 90 vs. placebo	Comparison groups	MK-3222 100 mg vs placebo	MK-3222 200 mg vs. placebo
		Difference	37.5%	35.3%
		95%-CI	31.1-43.4%	29.2-41.1%
		P-value	< 0.001	< 0.001

	PASI 75 week 12 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	13.1%%	17.4%
		95%-CI	5.3-20.7%	9.7-24.9%
		P-value	n.s.*	< 0.001
	PGA week 12 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	7.3%	11.7%
		95%-CI	-0.5-15.0%%	4.0-19.3%
		P-value	0.066 (n.s.*)	0.003
	PASI 75 week 28 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	20.1%	19.2%
		95%-CI	12.4-27.6%%	11.5-26.7%
		P-value	n.s.*	< 0.001
	PGA week 28 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	19.6%	24.1%
		95%-CI	11.7-27.3%	16.2-31.7%
		P-value	n.s.*	< 0.001
	PASI 100 vs placebo	Comparison groups	MK-3222 100 mg vs placebo	MK-3222 200 mg vs. placebo
		Difference	12.4%	11.7%
		95%-CI	8.5-16.6%	7.8-16.0%
		P-value	n.s.*	< 0.001
	PASI 90 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	17.4%	15.2%
		95%-CI	10.3-24.4%	8.3-22.1%
		P-value	n.s.*	n.s.*
	PASI 100 vs etanercept	Comparison groups	MK-3222 100 mg vs etanercept	MK-3222 200 mg vs. etanercept
		Difference	7.6%	7.0%
		95%-CI	3.3-12.3%	2.8-11.6%
		P-value	n.s.*	n.s.*
Notes	n.s.* - statistically not significant according to the pre-specified testing procedure Based on the pre-specified testing strategy, a statistically significant superiority of tildrakizumab 200mg over placebo could be shown for PASI 90 and PASI 100 at week 12. With regard to PASI 75 and PGA at week 12 tildrakizumab 200mg was also statistically significant superior to etanercept. With regard to PASI 90 and PASI 100, following the testing strategy the trial failed to show a statistically significant superiority of tildrakizumab 200 mg over etanercept. For tildrakizumab 100mg a statistically significant superiority with regard to PASI 90 at week 12 over placebo could be shown. Due to the testing strategy all other comparisons of tildrakizumab to placebo or etanercept with regard to key secondary endpoints failed.			

Children and Adolescent

All patients in the Phase 2b/3 trials were at least 18 years of age, and there have been no clinical trials conducted in the paediatric patient population to evaluate PK, safety or efficacy.

Elderly

A total of 175 patient´s ≥65 years old (155 patients aged between 65 and 75 and 20 patients ≥75 years old) were included in the clinical trial programme. Subgroup analyses were performed showing no meaningful difference in PASI 75 at week 12 for the tildrakizumab 200 mg group. A slight difference was seen for the tildrakizumab 100 mg group in study P011 with a higher proportion of patients in the <65 years of age group achieving a PASI 75 response. However, the number of patients included in this subgroup analysis was low.

Pregnant and breast feeding women

Female patients who were pregnant or lactating were excluded from enrolment in the clinical trials.

Patients with hepatic impairment

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted. Patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. Among patients receiving tildrakizumab during the base period, there were 90 patients with medical history of hepatic impairment in the Phase 2b/3 trials.

Patients with renal impairment

No formal trials with tildrakizumab on patients with renal impairment have been conducted. Patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials. At baseline, there were 609 patients with mild renal impairment, 56 patients with moderate renal impairment and 1 patient with severe renal impairment. There were no patients with renal failure included.

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

Cross-study comparisons of efficacy focused on the results through Week 12 to include data from the Pivotal Phase 3 trials and the Dose Ranging Study, due to the design of the studies. Summary of response rates beyond week 28 included the phase 3 studies with regards to PASI 75, PASI 90, PASI 100 and PGA at different timepoints to show the magnitude of treatment effect and time to onset of efficacy and response. The results of the pooled analysis for the Phase 2b/3 and Phase 3 studies show the favourable efficacy of tildrakizumab 200 mg in the with regards to PASI 75, 90, 100 and PGA as well as patient reported outcomes e.g. DLQI compared to tildrakizumab 100 mg, placebo and etanercept over time and across the studies. The results are in line with the ones seen in each study.

Table 23: Analysis of Subjects with PASI 75 Response at Week 12 Phase 2 and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set (Missing=NR)

Treatment	N	n	(%)	Difference vs. Placebo			Difference vs. Etanercept 50 mg	
				Estimate	95% CI†	p-value	Estimate	95% CI†
Placebo	355	20	(5.6)					
MK-3222 100 mg	705	439	(62.3)	56.4	(51.8, 60.7)	<.0001	13.1	(5.3, 20.7)
MK-3222 200 mg	708	459	(64.8)	59.3	(54.8, 63.4)	<.0001	17.4	(9.7, 24.9)
Etanercept 50 mg	313	151	(48.2)					

†based on Miettinen and Nurminen method stratified by trial, body weight (<=90kg, >90kg), and prior exposure to biologic therapy for psoriasis (yes/no).
N = number of subjects in the population; n = number of responders; (%) = 100*n/N.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.
NR=Non responder imputation

Table 24: Proportion of Subjects With PASI 75 Response at Week 12 Comparison to Etanercept (Missing=NR) (Full Analysis Set) Part 1 (P011)

Statistics	Placebo N=156	MK-3222 100 mg N=307	MK-3222 200 mg N=314	Etanercept N=313
PASI 75 (Week 12)				
Subjects with data	156	307	314	313
Responders (%)[†]	9 (5.8)	188 (61.2)	206 (65.6)	151 (48.2)
Difference in % vs. Etanercept (95% CI)[‡]		13.1 (5.3, 20.7)	17.4 (9.7, 24.9)	
p-Value[§]		0.001	<0.001	

Table 25: Proportion of Subjects with PASI 75 Response at Week 28 Missing=NR) (Full Analysis Set) Subjects Randomized to MK-3222 100 mg, MK-3222 200 mg, or Etanercept in Part 1 (P011)

Statistics	MK-3222 100 mg N=294	MK-3222 200 mg N=299	Etanercept N=289
PASI 75 (Week 28)			
Subjects with data	294	299	289
Responders (%)[†]	216 (73.5)	217 (72.6)	155 (53.6)
Difference in % vs. Etanercept (95% CI)[‡]	20.1 (12.4, 27.6)	19.2 (11.5, 26.7)	
p-Value[§]	<0.001	<0.001	

Table 26: Analysis of Subjects with PASI 90 Response at Week 12 Phase 2 and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set (Missing=NR)

Treatment	N	n	(%)	Difference vs. Placebo			Difference vs. Etanercept 50 mg	
				Estimate	95% CI†	p-value	Estimate	95% CI†
Placebo	355	7	(2.0)					
MK-3222 100 mg	705	253	(35.9)	33.8	(29.7, 37.8)	<.0001	17.4	(10.3, 24.4)
MK-3222 200 mg	708	262	(37.0)	35.0	(30.9, 38.9)	<.0001	15.2	(8.3, 22.1)
Etanercept 50 mg	313	67	(21.4)					

†based on Miettinen and Nurminen method stratified by trial, body weight (<=90kg, >90kg), and prior exposure to biologic therapy for psoriasis (yes/no).
N = number of subjects in the population; n = number of responders; (%) = 100*n/N.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.
NR=Non responder imputation

Table 27: Analysis of Subjects with PASI 100 Response at Week 12 Phase 2 and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set (Missing=NR)

Treatment	N	n	(%)	Difference vs. Placebo			Difference vs. Etanercept 50 mg	
				Estimate	95% CI†	p-value	Estimate	95% CI†
Placebo	355	2	(0.6)					
MK-3222 100 mg	705	93	(13.2)	12.6	(9.8, 15.4)	<.0001	7.6	(3.3, 12.3)
MK-3222 200 mg	708	91	(12.9)	12.2	(9.6, 15.0)	<.0001	7.0	(2.8, 11.6)
Etanercept 50 mg	313	15	(4.8)					

†based on Miettinen and Nurminen method stratified by trial, body weight (<=90kg, >90kg), and prior exposure to biologic therapy for psoriasis (yes/no).
N = number of subjects in the population; n = number of responders; (%) = 100*n/N.
CI = Confidence interval; PASI = Psoriasis Area and Severity Index.
NR=Non responder imputation

Table 28: Analysis of Subjects with PGA 'Clear' or 'Minimal' Response at Week 12 Phase 2 and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set (Missing=NR)

Treatment	N	n	(%)	Difference vs. Placebo			Difference vs. Etanercept 50 mg	
				Estimate	95% CI†	p-value	Estimate	95% CI†
Placebo	355	20	(5.6)					
MK-3222 100 mg	705	403	(57.2)	51.3	(46.7, 55.7)	<.0001	7.3	(-0.5, 15.0)
MK-3222 200 mg	708	425	(60.0)	54.4	(49.8, 58.6)	<.0001	11.7	(4.0, 19.3)
Etanercept 50 mg	313	149	(47.6)					

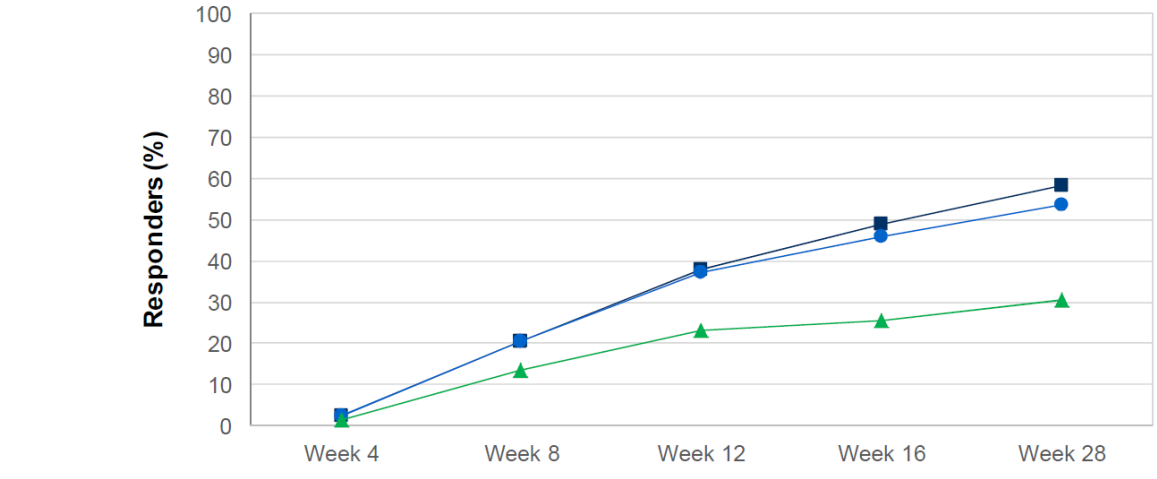
†based on Miettinen and Nurminen method stratified by trial, body weight (<=90kg, >90kg), and prior exposure to biologic therapy for psoriasis (yes/no).
N = number of subjects in the population; n = number of responders; (%) = 100*n/N.
CI = Confidence interval; PGA = Physician Global Assessment.
NR=Non responder imputation

Table 29: Summary of Response Rates over Time Phase 3: 28-Week Active Treatment Efficacy Pool Full Analysis Set

Treatment	N	PASI 75		PASI 90		PASI 100		PGA 'clear' or 'minimal'		
		n	(%)	n	(%)	n	(%)	N	n	(%)
Week 4										
MK-3222 100 mg	610	72	(11.8)	14	(2.3)	4	(0.7)	606	94	(15.5)
MK-3222 200 mg	611	72	(11.8)	14	(2.3)	5	(0.8)	607	101	(16.6)
Etanercept 50 mg	306	30	(9.8)	4	(1.3)	0	(0.0)	304	41	(13.5)
Week 8										
MK-3222 100 mg	603	270	(44.8)	123	(20.4)	39	(6.5)	601	274	(45.6)
MK-3222 200 mg	599	264	(44.1)	122	(20.4)	33	(5.5)	593	271	(45.7)
Etanercept 50 mg	298	109	(36.6)	40	(13.4)	9	(3.0)	295	114	(38.6)
Week 12										
MK-3222 100 mg	598	385	(64.4)	226	(37.8)	81	(13.5)	598	347	(58.0)
MK-3222 200 mg	602	398	(66.1)	224	(37.2)	80	(13.3)	597	368	(61.6)
Etanercept 50 mg	288	151	(52.4)	67	(23.3)	15	(5.2)	286	149	(52.1)
Week 16										
MK-3222 100 mg	583	427	(73.2)	267	(45.8)	101	(17.3)	580	361	(62.2)
MK-3222 200 mg	593	443	(74.7)	290	(48.9)	127	(21.4)	586	375	(64.0)
Etanercept 50 mg	283	162	(57.2)	72	(25.4)	19	(6.7)	281	143	(50.9)
Week 28										
MK-3222 100 mg	575	445	(77.4)	308	(53.6)	133	(23.1)	575	378	(65.7)
MK-3222 200 mg	581	453	(78.0)	339	(58.3)	170	(29.3)	578	406	(70.2)
Etanercept 50 mg	277	155	(56.0)	85	(30.7)	31	(11.2)	274	131	(47.8)

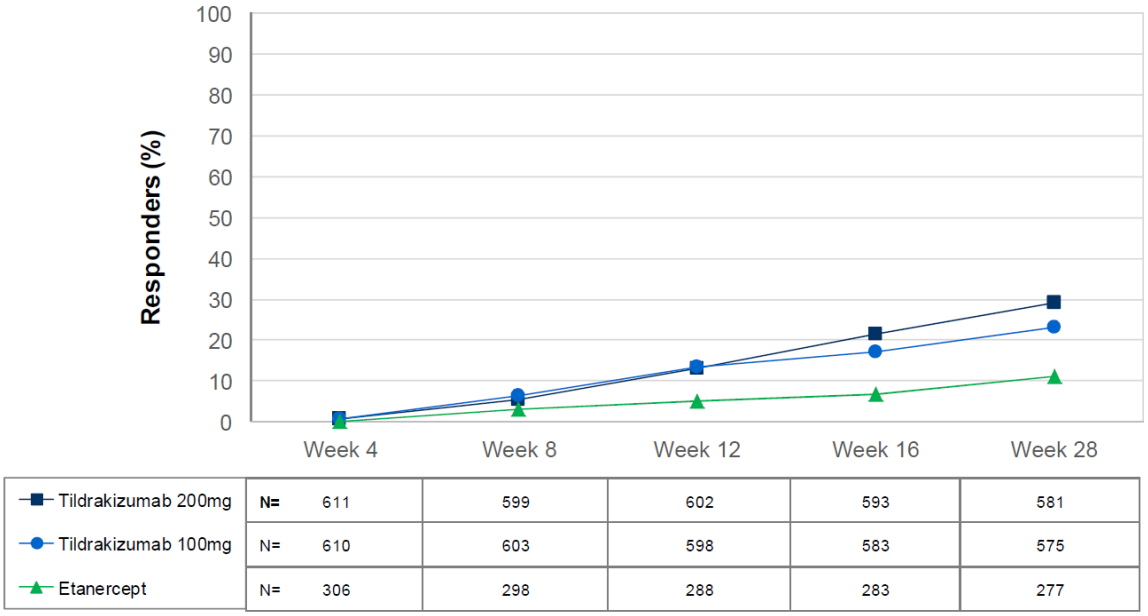
N = number of subjects with data at particular weeks; n = number of responders; (%) = 100*n/N.

Figure 18: Response Rates Over Time - PASI 90 Phase 3: 28-Week Active Treatment Efficacy Pool Full Analysis Set (Observed Data Only)



Tildrakizumab 200mg	N= 611	599	602	593	581
Tildrakizumab 100mg	N= 610	603	598	583	575
Etanercept	N= 306	298	288	283	277

Figure 19: Response Rates Over Time - PASI 100 Phase 3: 28-Week Active Treatment Efficacy Pool Full Analysis Set (Observed Data Only)



Tildrakizumab 200mg	N= 611	599	602	593	581
Tildrakizumab 100mg	N= 610	603	598	583	575
Etanercept	N= 306	298	288	283	277

Table 30: PASI Response Rates and PASI Percent Change from Baseline in Phase 3 studies at Week 52 (P010 and P011) and Week 64 (P010) – Side-by-Side (Full Analysis Set) Subjects Randomized to MK-3222 100mg or MK-3222 200mg in Part 1 Who Were PASI 75 Responders at Week 28

		100mg		200mg	
Outcome	**Week**	**P010 R**	**P011 R**	**P010 R**	**P011 R**
PASI 75 (%)	52	86.7 (98/113)	93.6 (191/204)	91.2 (103/113)	97.1 (102/105)
	64	87.5 (98/112)	-	93.9 (107/114)	-
PASI 90 (%)	52	63.7 (72/113)	78.4 (160/204)	69.9 (79/113)	81.7 (86/105)
	64	58 (65/112)	-	74.6 (85/114)	-
PASI 100 (%)	52	32.7 (37/113)	35.3 (72/204)	43.4 (49/113)	46.7 (49/105)
	64	32.1 (36/112)	-	40.4 (46/114)	-
PASI % change from BL	52	-88.9 (n=113)	-93.4 (n=204)	-91.7 (n=113)	-94.6 (n=105)
	64	-88.4 (n=112)	-	-93.1 (n=114)	-

R:PASI 75 Responders at Week 28.

Improvement in DLQI

The data for patients with a DLQI score of 0 or 1 (no impact at all of psoriasis on their life) at Weeks 12 and 28 were pooled for the Phase 3 trials, P010 and P011.

The results show, that the proportion of patients with DLQI score of 0 or 1 at Week 12 was greater in the tildrakizumab 100-mg and 200-mg groups compared with the placebo group in both P010 and P011 and compared with the etanercept group in P011. In addition the 200mg groups in both trials had numerically greater responses compared with the 100mg groups at Week 12 and Week 28. In P011, the 100-mg, 200-mg, and placebo to 200-mg groups had a higher proportion of patients with DLQI score of 0 or 1, compared with the etanercept group.

Table 31: DLQI Score week 12 and week 28

	P010						P011					
Treatment	N	DLQI Score of 0 or 1		DLQI Score of 1		DLQI Score of 0	N	DLQI Score of 0 or 1		DLQI Score of 1		DLQI Score of 0	
		n	(%)	n	(%)	n (%)		n	(%)	n	(%)	n	(%)
Week 12													
Placebo	150	8	(5.3)	5	(3.3)	3 (2.0)	150	12	(8.0)	6	(4.0)	6	(4.0)
MK-3222 100 mg	304	126	(41.4)	63	(20.7)	63 (20.7)	296	119	(40.2)	46	(15.5)	73	(24.7)
MK-3222 200 mg	299	132	(44.1)	60	(20.1)	72 (24.1)	306	145	(47.4)	45	(14.7)	100	(32.7)
Etanercept	NA						304	108	(35.5)	52	(17.1)	56	(18.4)
Week 28													
Placebo to MK-3222 100 mg	71	37	(52.1)	13	(18.3)	24 (33.8)	68	26	(38.2)	8	(11.8)	18	(26.5)
Placebo to MK-3222 200 mg	68	38	(55.9)	17	(25.0)	21 (30.9)	69	39	(56.5)	15	(21.7)	24	(34.8)
MK-3222 100 mg	290	152	(52.4)	61	(21.0)	91 (31.4)	290	157	(54.1)	55	(19.0)	102	(35.2)
MK-3222 200 mg	289	164	(56.7)	56	(19.4)	108 (37.4)	297	193	(65.0)	62	(20.9)	131	(44.1)
Etanercept	NA						282	111	(39.4)	41	(14.5)	70	(24.8)

N = Number of randomized subjects who received at least one dose of trial medication in study part and with valid value at the time point for endpoint.
n = the number of responders at the visit.
NA = not applicable. P010 trial did not include etanercept treatment.
DLQI = Dermatology Life Quality Index.
No imputation of missing data.

Dose Increase Effect in Partial Responders

The dose increase effect from Week 28 to Week 52 for partial responders on tildrakizumab 100mg (subjects reaching PASI 50 but not PASI 75 at Week 28) was assessed using data pooled across the Phase 3 trials (P010 and P011) for the proportion of subjects with PASI 75, 90 and 100 responses. Due to the small sample sizes of each treatment group (n=40 for subjects having continued beyond Week 28 with 100mg and n=40 for subjects having received an increased dose of 200mg), results should be interpreted with caution, in particular for lower responsive PASI thresholds (PASI 90 and PASI 100).

At Week 52, after 24 weeks of treatment beyond Week 28 (and two doses of tildrakizumab), the majority of subjects who were partial responders to tildrakizumab 100mg at Week 28 and continued treatment with 100mg or increased to 200mg had reached PASI 75: 57.5% for subjects who remained on 100 mg and 60.0% for subjects who increased dose to 200mg.

Higher PASI improvements to PASI 90 and PASI 100 were also achieved: 11/40 (27.5%) and 6/40 (15.0%) had reached PASI 90 in the continuing 100mg and increasing to 200mg groups respectively 7/40 (17.5%) and 2/40 (5.0%) had reached PASI 100 in the continuing 100mg and increasing to 200mg groups respectively.

Patients with high body weight and with higher disease burden

Additionally, during the assessment, the applicant provided further data on patients with higher disease burden and body weight. The CHMP agreed that these data could be supportive of a recommendation of 200 mg dose regimen in these patients in order to achieve higher efficacy. A specific recommendation was introduced for these subpopulations.

Figure 20: Efficacy at week 28 by weight and baseline PASI- pooled data

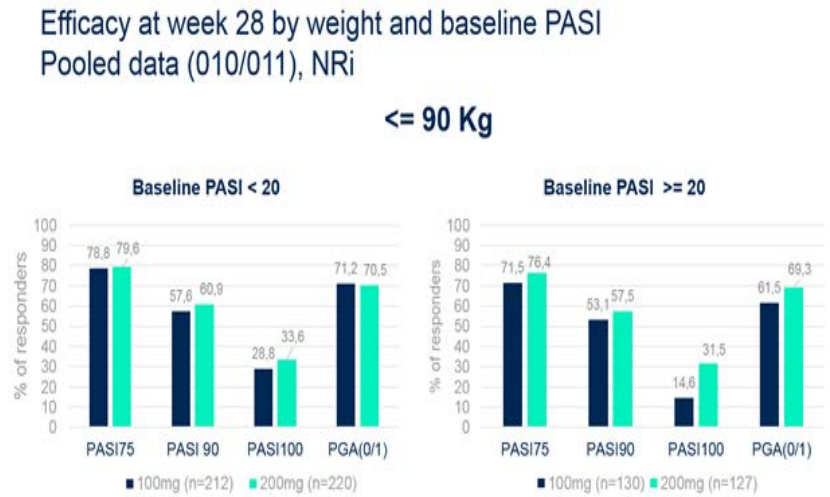
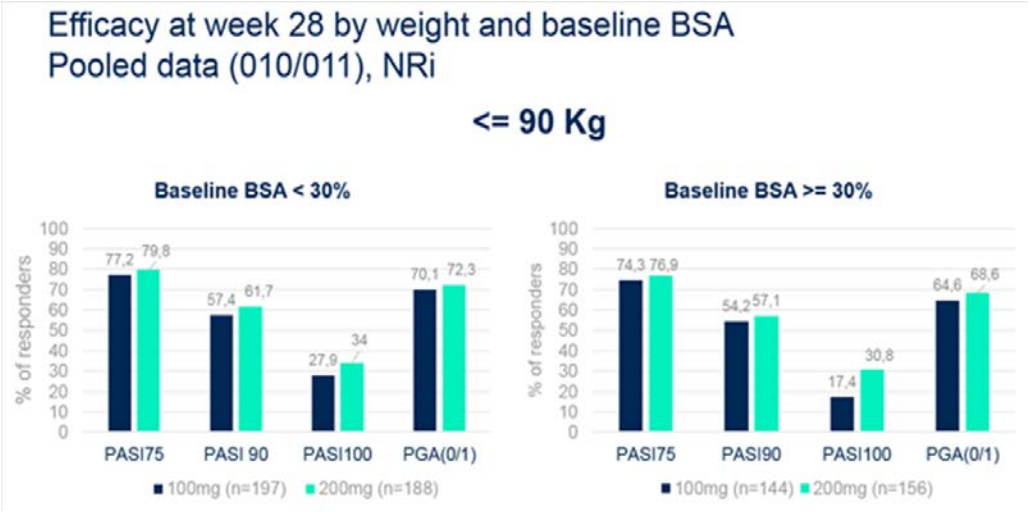


Figure 21: Efficacy at week 28 by weight and baseline BSA- pooled data



ADA

Phase 2b or Phase 3 subjects treated continuously with tildrakizumab 100mg or 200mg in the TE-POS NAb positive (NAb-POS) category represented a small proportion, ~0.6% (8/1400) and 2.8% (22/780), of the evaluable population, through 12/16 weeks and through 52/64 weeks, respectively.

Effect of ADA on Efficacy Endpoints- Treatment Emergent ADA Positive Subjects Compared to Negative and Inconclusive (Combined) at 12 Weeks in Phase 2b and Phase 3

The proportion of subjects in Phase 2b and Phase 3 randomized to 100 mg and 200 mg in Part 1 who were categorized as TE-POS ((NAb-POS and NAb-NEG combined) who achieved PASI 75, PASI 90, PASI 100, or PGA was similar to the proportion of subjects who were categorized as negative and inconclusive (combined) at Week 12.

Effect of ADA on the Percent Improvement in PASI Score through Week 12 by ADA Subject Category in Phase 2b and Phase 3

In subjects treated with 100mg, the percent improvement in PASI score at Week 12 was similar for negative, inconclusive, Non-TE-POS NAb NEG, and TE-POS NAb-NEG subjects (75%, 80%, 76%, and

79%, respectively); Non-TE-POS NAb-POS and TE-POS NAb-POS subjects showed a marginally lower percent improvement (68% and 62%) in PASI score at Week 12. For subjects treated with 200 mg that were TE-POS NAb-POS (N=4), the percent improvement in PASI score was less (38%) relative to negative subjects (76%); and other positive subject categories showed PASI improvements which were comparable to negative subjects (range 81%-88%). The number of TE-POS NAb-POS subjects for the 100 mg and 200 mg dose groups was small (N=4 for each dose levels), and caution should be exercised regarding interpretation.

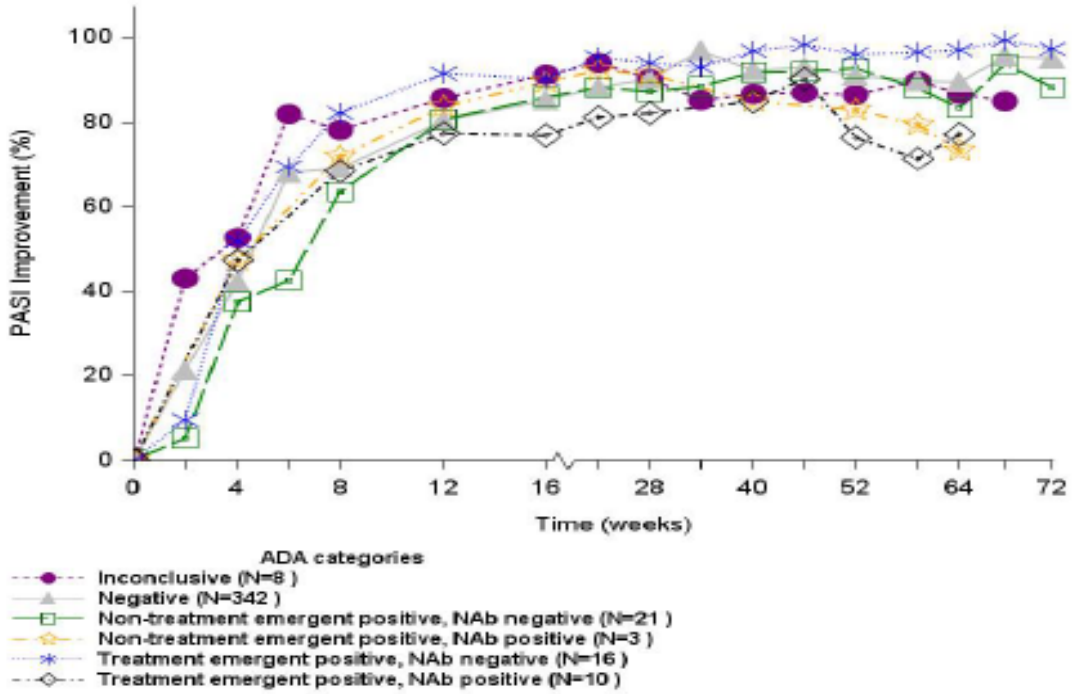
Moreover, the subjects in the negative and inconclusive categories showed similar percent improvement in PASI scores at Week 12, 75% and 80%, respectively, for 100 mg and 76% and 79%, respectively, for 200 mg.

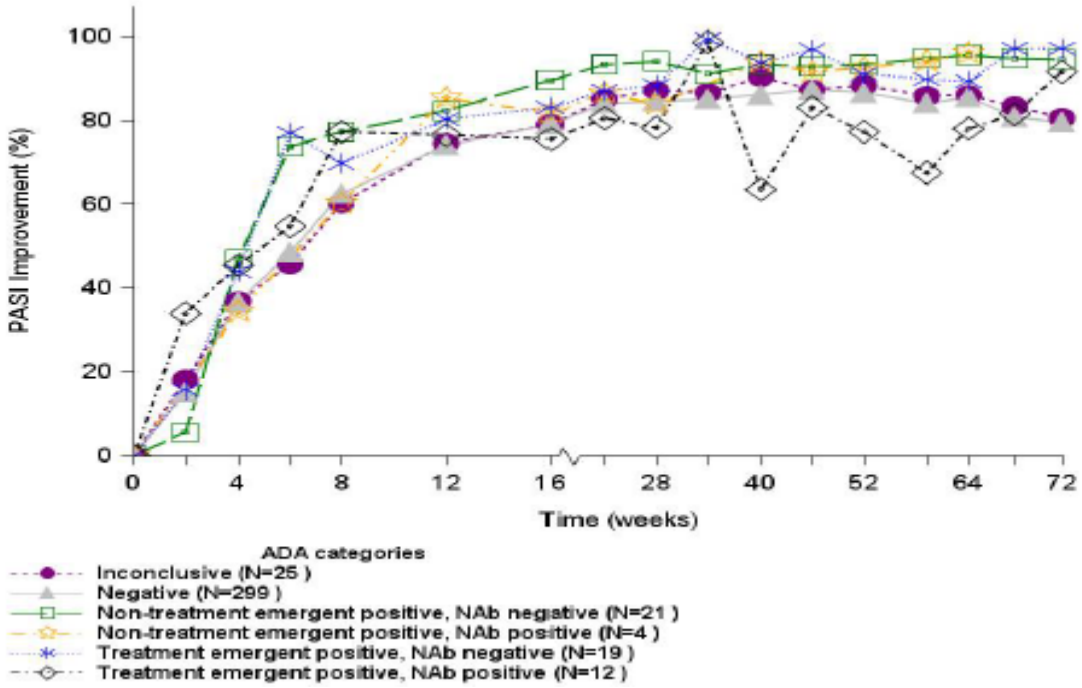
Effect of ADA on the Percent Improvement in PASI Score for the Full Duration of Trials by ADA Subject Category in Phase 2b and Phase 3

The percent improvement of PASI score at Week 52 in subjects on 200 mg continuously was less for TE-POS NAb-POS subjects (77%) as compared to negative subjects (87%) and other positive categories (range 91% to 94%) For the percent improvement in PASI score at Week 52, it is worth noting that the number of TE-POS NAb-POS subjects with PASI data for the 100 mg and 200 mg groups was small (N=10 and N=12, respectively) and considerable caution should be exercised regarding interpretation.

Notably, there was no difference between negative and inconclusive subjects with regard to PASI score improvement at Week 52; 91% and 86%, respectively for 100 mg and 87% and 88% for 200 mg, respectively. Note that, the number of inconclusive subjects was also small at the end of the trials, N=8 and N=25 for 100 mg and 200 mg, respectively.

Figure 22: Effect of ADA on Percent PASI Improvement in Subjects on 100 mg (above) or 200 mg (below) Tildrakizumab for the Full Duration of the Trials by ADA Subject Category in Phase2b and Phase 3





The numbers of patients who were ADA positive is rather low in both groups however it is seen that patients who were TE –POS Nab POS had lower PASI 75 and PGA responses at week 52 and lower PGA responses compared with those who were Nab negative in both treatment arms. It is not clear whether the true incidence of ADA's is clear as the serum level of Tildrakizumab affected the ADA assay, this could be more relevant for the higher dose of 200mgs.

Supportive study(ies)

N/A

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of Tildrakizumab is substantiated by a comprehensive data package that included one Phase 2b trial (P05495) and 2 Phase 3 trials (P010 and P011). These clinical studies were randomized, double-blind, placebo-controlled, multi-center trial conducted in adults ≥ 18 years of age with moderate-to-severe chronic plaque psoriasis, who were candidates for phototherapy or systemic therapy.

The development was in line with the CHMP Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02 corr, effective June 2005). All clinical studies were GCP-compliant.

The Phase 2b study (**P05495**) was a dose ranging study to identify the optimal SC dosing regimen for tildrakizumab. The trial consisted of 3 parts: Part 1 was a 16-week, double-blind, placebo-controlled, treatment period to evaluate the optimal dose regimen (5 mg, 25 mg, 100 mg, or 200 mg against placebo) for induction of response (Weeks 0 to 16), Part 2 was a 36-week, double-blind, treatment period to evaluate the optimal dose regimen for maintenance of response (Weeks 16 to 52), and Part 3 was a 20-week washout period (Weeks 52 to 72).

The Phase 3 trials were designed to demonstrate the efficacy of tildrakizumab compared to placebo (Study P010 and P011) and/or an active comparator (Study P011).

Study P010 was placebo-controlled and randomized 772 patients. The duration of the base study was up to 88 weeks for each subject. This included a 4-week screening period, a 12-week Part 1 period (Week 0 to Week 12), a 16-week Part 2 period (Week 12 to Week 28), a 36-week Part 3 period (Week 28 to Week 64), and a 20-week follow-up period. In Part 1 patients were randomized on Day 1 to receive Tildrakizumab 200 mg subcutaneously (Arm A), Tildrakizumab 100 mg (Arm B) or Tildrakizumab placebo (Arm C). In Part 2 patients initially randomized to placebo (Arm C) were re-randomized to receive either tildrakizumab 200 or 100 mg at Week 12 and 16. In Part 3 incorporated randomized withdrawal and retreatment design elements from week 28 and beyond, to formally assess the efficacy and safety of tildrakizumab maintenance dosing relative to the withdrawal of treatment in PASI 75 responders. Upon completion of Part 3, patients who were eligible may have entered the long-term safety extension study that will assess the long-term safety/tolerability of tildrakizumab.

In **Study P011** the duration of the base study was up to 76 weeks for each patient. This was the only study in the development program of tildrakizumab, which used etanercept as comparator. It consisted of a 4-week screening period, a 12-week Part 1 period, a 16-week Part 2 period and a 24-week Part 3 period. In Part 1 patients were randomized to receive tildrakizumab 200 mg (Arm A), tildrakizumab 100 mg (Arm B), placebo (Arm C) or etanercept (Arm D). At Week 12, all patients initially randomized to placebo (Arm C) were re-randomized to receive tildrakizumab 100 mg or tildrakizumab 200 mg. At week 28 responders in Arm A were re-randomized in a 1:1 ratio to tildrakizumab 200 mg or tildrakizumab 100 mg, Responders in Arm B continued to receive tildrakizumab 100 mg. Partial-responders in Arm A continued to receive tildrakizumab 200 mg, while in Arm B they were re-randomized in a 1:1 ratio to tildrakizumab 100 mg or tildrakizumab 200 mg. Partial responders and non-responders in Arm D were assigned to receive tildrakizumab 200 mg. Responders in Arm D were discontinued.

Patients selected for the studies were adult males and females 18 years of age or older with a diagnosis of plaque psoriasis for more than 6 months and were candidates for phototherapy or systemic therapy. Disease severity was gated to moderate to severe by baseline scores of BSA involvement ≥10%, PASI score ≥12, PGA of at least moderate disease (≥3). This is in line with the CHMP guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr). The exclusion criteria were designed to ensure patients safety. Excluded were patients with any infection including HIV, HCV and HBV, malignancies, hospitalisation due to CV events within 6 months and other organ dysfunctions. The eligibility criteria are adequate for a patient population with moderate to severe plaque psoriasis.

The design of the studies, especially P011 was complex and included an active comparator, multiple re-randomization and withdrawal and retreatment arms, leading to high numbers of placebo injections needed to keep the blind. This can be considered to be the reason for the high number of protocol deviations in the category of study drug administration. However, the study design resulted in a good overview of the product characteristics for use in the clinical setting.

In study P010 major protocol deviations were reported at a greater incidence in the informed consent category for 32.1% of patients. In Study P011 major deviations were reported for informed consent (326 deviations), investigational product administration or study treatment (240 deviations) and procedures or tests (212 deviations) category. Additionally, 175 patients have been excluded from the PP analysis population in this study mainly due to violations regarding the eligibility criteria related to the disease severity (i.e. PASI, PGA or BSA). GCP inspections for both pivotal phase 3 studies have been performed. The applicant provided additional sensitivity analyses excluding those entries in order to quantify the relevance of these entries on the results of each study. There were 2 approaches, in

which affected entries have been considered as “Non-responder” or all patients with any entry affected have been excluded from the analyses. The results of these analyses showed only small differences regarding the results of the co-primary endpoints (PASI75 and PGA response).

In study P011, there were high numbers of protocol deviations. The most common deviations were informed consent, administration of study drug and test or procedures. Although the applicant states that no patients were included in the study without a signed informed consent prior to participation. A total of 175 patients were excluded from the PP analysis population in Part 1 (N=140) or Part 2 (N=167) of the base study. The most common reason patients were excluded from the PP population was due to not meeting the PASI, PGA, or BSA inclusion criteria. GCP inspections for both pivotal phase 3 studies have been performed. Additional sensitivity analyses were presented by the applicant demonstrating that the protocol deviations in both studies had no meaningful effect on the results of the co-primary endpoints.

Re-treatment with tildrakizumab after relapse was also effective. Patients who were re-treated after relapse during the withdrawal phase responded to re-initiation of their initial treatment.

Efficacy data and additional analyses

The median baseline PASI and PGA score was similar across all treatment groups. Thirty five point eight percent (35.8%) of the patients had received prior phototherapy, 41.1% had received prior conventional systemic therapy, 17.5% had received prior biologic therapy for the treatment of psoriasis, and 8.3% had received at least one anti-TNF alpha agent. A total of 15.4% of study patients had a history of psoriatic arthritis.

Patients were not allowed concomitant moderate to high potency topical steroids or systemic steroids which may be useful in practice, it is unclear whether any additional benefit would be demonstrated or indeed safe to use tildrakizumab in combination with these medicinal products.

The results of the Phase 2b dose ranging study **P05495** show a dose-dependent, statistically significant improvement in PASI score. With regards to the primary endpoint the highest percentage of patients achieved a PASI 75% response at week 16 in the tildrakizumab 200 mg with 74.42%, followed by the tildrakizumab 100 mg group 66.29% compared to placebo with 4.44%. Similar results are shown by the key secondary endpoints. Therefore, the selection of the tildrakizumab 200 and 100 mg for the evaluation in the pivotal phase 3 studies is conclusive.

The proportion of patients in Study **P010** achieving a PASI 75 response at Week 12 was significantly higher in the tildrakizumab 100 mg (63.8%) and tildrakizumab 200 mg (62.3%) groups compared with the placebo (5.8%) group ($p<0.001$ each). Regarding the second co-primary endpoint, the proportion of patients with a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12 was significantly greater in the tildrakizumab 100 mg (57.9%) and tildrakizumab 200 mg (59.1%) groups compared with the placebo (7.1%) group ($p<0.001$ each). The key secondary endpoints PASI 90 and 100 at week 12 as well as the other secondary endpoints support the efficacy shown for the co-primary endpoints.

The proportion of patients in Study **P011** achieving a PASI 75 response at Week 12 was significantly greater in the tildrakizumab 100 mg (61.2%) and tildrakizumab 200 mg (65.6%) groups compared with the placebo (5.8%) and the etanercept (48.2%) group ($p<0.001$ each). Regarding the second co-primary endpoint, the proportion of patients with a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12 was significantly greater in the tildrakizumab 100 mg (54.7%) and tildrakizumab 200 mg (59.2%) groups compared with the placebo (4.5%) and etanercept

(47.6%) group (p<0.001 each). The key secondary endpoints PASI 90 and 100 at week 12 as well as the other secondary endpoints support the efficacy shown for the co-primary endpoints.

The onset of efficacy is not as fast compared to recently approved Il-17 inhibitors showing the best results for PASI 100 not earlier as week 44.The difference between the tildrakizumab dosing groups was small at the beginning of the treatment resulting in similar efficacy results. At week 16 the tildrakizumab 200 mg group begins to show slightly higher efficacy with regards to PASI 75, 90 and 100. Although, the response rates over time are favorable for both doses. The rate of PASI 75 responders remained over 90% from week 32 onward with 95.5% for the 100 mg and 98.3% for the 200 mg tildrakizumab group at week 32. The rate of PASI 100 responders at week 36 reached 40.2% in the tildrakizumab 200mg continuous group and 36.8% in the tildrakizumab 100 mg continuous group.

In Study P011, the efficacy of tildrakizumab in etanercept non-responders was evaluated. Patients who were classified as non-responder or partial-responder (did not reach PASI 75 on etanercept at Week 28) were switched to Ilumya 200 mg after a washout period of 4 weeks. After 3 doses of tildrakizumab 200 mg (Week 52), 81.4% had achieved PASI 75 response.
Overall, since there was no significant difference in efficacy among the two dose regimen, the CHMP considered more adequate to recommend the lower dose regimen, i.e. 100 mg.

Additionally, during the assessment, the applicant provided further data on patients with higher disease burden and body weight. The CHMP agreed that these data could be supportive of a recommendation of 200 mg dose regimen in these patients in order to achieve higher efficacy. A specific recommendation was introduced for these subpopulations.

2.5.2. Conclusions on clinical efficacy

Tildrakizumab demonstrated superior efficacy to placebo in phase 2b and in the phase 3 clinical studies. The 100mg and 200mg doses carried forward to phase 3 studies are considered generally justified.

The results of the pivotal phase 3 studies show that tildrakizumab is effective in improving clinically relevant sign and symptoms of patient with plaque psoriasis. The proportion of patients achieving PASI 75, 90, 100 and PGA response at different time points was higher in the tildrakizumab treatment groups compared to placebo and etanercept. The CHMP considered more appropriate to recommend the lower dosing regimen of tildrakizumab of100 mg at weeks 0, 4 and every 12 weeks thereafter. However, based on the efficacy and PK data, recommendation of 200mg for higher weight patients (>90 kg) and for patients with higher disease burden was further discussed and the CHMP agreed that it may be recommended in these patients. This is reflected in the posology section of the SmPC.

2.6. Clinical safety

The clinical development program included evaluations of tildrakizumab (also known as MK-3222 and SCH900222) across 9 completed trials: 6 Phase 1 trials - 3 in healthy subjects (P05661, P05776, P06306), 2 in subjects with moderate-to-severe plaque psoriasis (P05382 and P009), and 1 in subjects with Crohn's disease (P05839). There was one Phase 2b trial - P05495 (P003) and two Phase 3 trials - P010 and P011. The Phase 1 trials enrolled healthy subjects (P05661, P05776, and P06306), patients with moderate-to-severe plaque psoriasis (P05382 and P009) and patients with active Crohn's disease (P05839). The Phase 2b and Phase 3 trials were conducted in the target subject population with moderate-to-severe chronic plaque psoriasis. With the response to D120 LoQ the applicant submitted new safety data for the long term extension study up to a cut-off date of 27 May 2017.

For the Phase 1 trials the demographic data, exposure data, and AE summary data have b

een integrated as follows to facilitate the comparison of the short-term safety profile for tildrakizumab:

- Integrated AE data from 3 trials in healthy subjects (P05661, P05776, and P06306).
- Integrated AE data from 2 trials in subjects with moderate-to-severe plaque psoriasis (P05382 and P009).
- AE data from the Crohn's Disease trial (P05839).

For the Phase 2b (P05495) and Phase 3 trials (P010, P011), the demographic data, exposure data, and AE summary data have been integrated to facilitate the comparison of the long-term safety profile for tildrakizumab. These trials were similar in study design and eligibility criteria, but differed by study duration and dose groups. The safety data from Phase 2b and Phase 3 trials were integrated and analysed using the following 2 general analytical approaches:

- Analyses of rates of AEs during the placebo-controlled periods of the trials.
- Analyses of rates of AEs over the entire base periods of the trials adjusted for duration of exposure (ie, per 100 subject-years of follow-up).

Patient exposure

A total of 1994 subjects with psoriasis received any dose of tildrakizumab at some point during the Phase IIb/III trial periods. The exposure to the drug is considered sufficient in accordance with the ICH E1 Guideline requirements ('The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions' CPMP/ICH/375/95). (42 patients received at least the 5 mg dose; 123 patients received at least the 25 mg dose; 1083 patients received at least the 100 mg dose; and 1041 patients received at least the 200 mg dose).

The mean duration of treatment was 53.9 weeks for tildrakizumab during the base trial periods, corresponding to an exposure of 2059.04 subject-years.

Table 32: Extent of Exposure to MK-3222 Phase 2 and 3 Trials - Base Period All Subjects as Treated

MK-3222	>0 to < 12 weeks	>=12 to < 28 weeks	>=28 to < 52 weeks	>=52 to < 64 weeks	>= 64 weeks	Total Subjects	Duration Range (weeks)	Mean Duration (weeks)	Total Exposure (subject-year)
Any Dose	32	72	499	223	1168	1994	4 to 88	53.9	2059.04
5 mg	2	27	3	0	10	42	4 to 64	27.7	22.31
25 mg	3	28	34	1	57	123	4 to 64	46.5	109.55
100 mg	6	122	413	98	444	1083	4 to 76	48.1	998.32
200 mg	21	81	423	106	410	1041	4 to 76	46.6	928.87

Each subject is counted once on each applicable dosage category row.

This table reflects transient cross-treatments.

For MK-3222, each priming dose is counted as 4 weeks of exposure and each subsequent dose is counted as 12 weeks.

Extent of Exposure to MK-3222 Phase 2 and 3 Trials - Base Period All Subjects as Treated (20 week follow up)

MK-3222	< 52 weeks	>= 52[a] weeks	>= 78[b] weeks	>= 104 weeks	Total Subjects	Duration Range (weeks)	Mean Duration (weeks)	Total Exposure (subject-year)
Any Dose	438	1556	1177	987	1994	4 to 184	91.7	3505.39
5 mg	32	10	0	0	42	4 to 64	27.7	22.31
25 mg	65	58	0	0	123	4 to 64	46.5	109.55
100 mg	411	672	587	469	1083	4 to 184	82.3	1708.96
200 mg	354	687	570	451	1041	4 to 184	83.4	1664.57

[a]:Includes subjects with exposure > 78 weeks and subjects with exposure > 104 weeks.
[b]:Includes subjects with exposure > 104 weeks.
[c] "Total Subjects" encompasses subjects with exposure <52 weeks and >= 52 weeks (subjects counted only once per dose/time).
The 20-week follow-up counts as exposure time.
Each subject is counted once on each applicable dosage category row.
This table reflects transient cross-treatments.
For MK-3222, each priming dose is counted as 4 weeks of exposure and each subsequent dose is counted as 12 weeks.

Regarding particular sub-groups, the exposure is low, however adequate in the elderly population (>65years of age). Exposure is inadequate in moderate to severe renal impairment, elderly >75years of age, immunocompromised subjects and subjects with hepatic impairment. There is inadequate data in pregnancy and lactation and the paediatric population. These sub-groups are represented accordingly in the SmPC.

New safety data from the long term extension study up to a cut-off date of 27 May-2017 were submitted with the responses to the D120 LoQ. Of the original 1236 subjects who were randomised to the 100 mg or 200 mg treatment arms in the preceding period of the studies, and continued on these treatments in the extension period, there were 620 subjects in the tildrakizumab100 mg arm and 616 subjects to the tildrakizumab 200 mg arm. Overall, of these 1236 original subjects, 1055 subjects were continuing at the time of the 27 May 2017 cut-off date, comprising 520 subjects in the 100 mg group and 535 in the 200 mg group: 181 subjects had discontinued.

Table 33: Updated Extent of exposure to tildrakizumab Phase 2 and 3 trials Base period and extension period (at 27 May 2017)

MK-3222	< 52 weeks	>= 52[a] weeks	>= 78[b] weeks	>= 104 weeks	Total Subjects	Duration Range (weeks)	Mean Duration (weeks)	Total Exposure (subject-year)
Any Dose	437	1557	1211	1152	1994	4 to 220	108.1	4130.24
5 mg	32	10	0	0	42	4 to 64	27.7	22.31
25 mg	65	58	0	0	123	4 to 64	46.5	109.55
100 mg	411	672	600	569	1083	4 to 220	97.9	2031.85
200 mg	353	688	604	576	1041	4 to 220	98.6	1966.54

[a]:Includes subjects with exposure > 78 weeks and subjects with exposure > 104 weeks.
[b]:Includes subjects with exposure > 104 weeks.
Each subject is counted once on each applicable dosage category row.
This table reflects transient cross-treatments.
For tildrakizumab, each priming dose is counted as 4 weeks of exposure and each subsequent dose is counted as 12 weeks.
Source: Table 2.7.4- 10

Pooling Strategy

The Pooling Strategy included different pools of safety data: Phase 2 and Phase 3: Placebo-controlled Safety Pool (16 weeks for P05495 and 12 weeks for P010 and P011), Phase 3: Placebo-controlled Safety Pool (12 weeks), Phase 2 and Phase 3: Base Period Safety Pool (52 weeks for P05495 and P011, and 64 weeks for P010)

Adverse events

Integrated data from the Phase 2b (P05495) and Phase 3 trials (P010, P011) were evaluated by the following two general analytical approaches:

- Analyses of percentages of pooled AEs during the placebo-controlled periods of the trials
- Analyses of rates of pooled AEs over the entire base period of the trials adjusted for duration of exposure (ie, per 100 subject-years of follow-up)

Phase 1 trials

Phase 1 trials, were conducted in healthy subjects (P05661, P05775, P06306), patients with moderate-to-severe psoriasis (P05382, P009) and patients with Crohn's Disease (P05389). More than 60% of participants in each study reported at least one Adverse Events. Common adverse events reported were headache with 27.2% in the healthy subjects, 17.3% in patients with psoriasis, 13% in patients with Crohn´s disease and infections with 27.2% in the healthy subjects, 14.7% in patients with psoriasis.

Study P010

During Part 1 of study P010, the proportion of patients with one or more adverse events was comparable between the treatment groups (48.1%, 47.2%, and 42.2% in the placebo, tildrakizumab 100 mg, and tildrakizumab 200 mg groups, respectively). Adverse events were reported most frequently for the Infections and Infestations SOC (20.4%), the proportion of patients with drug-related adverse events in Part 1 was similar between treatment groups (6.5%, 8.7%, and 7.8% in the placebo, tildrakizumab 100 mg, and tildrakizumab 200 mg groups, respectively). During Part 2, the proportion of patients with one or more adverse events was comparable between the 2 treatment groups (43.9% and 39.7% in the tildrakizumab 100 mg and tildrakizumab 200 mg groups, respectively). During Part 3, the proportion of patients with one or more adverse events was comparable between the 2 treatment groups (68.7% and 69.4% in the tildrakizumab 100 mg and

tildrakizumab 200 mg groups, respectively). After adjustment for exposure, the incidence rate of patients with one or more adverse events during the base study was comparable between the tildrakizumab 100 mg group and the tildrakizumab 200 mg group (72.9 and 73.3 patients with adverse events per 100 patient years, respectively). The incidence rate in the placebo group was higher with 128.3 patients with adverse events per 100 patient years. Similar to the individual parts of the base study, adverse events were reported most frequently for the Infections and Infestations SOC (73.8, 44.8, and 47.4 patients with adverse events per 100 patient years in the placebo, tildrakizumab 100 mg, and tildrakizumab 200 mg groups, respectively) and the most common adverse event was nasopharyngitis. The incidence rate of patients with drug-related adverse events during the base study was numerically greater in the placebo group compared with the tildrakizumab groups. After adjustment for exposure, the incidence rates of patients with drug-related adverse events during the base study were similar in the tildrakizumab 100 mg and tildrakizumab 200 mg groups (15.7 and 16.8 patients with adverse events per 100 patient years, respectively. The incidence rate in the placebo group was numerically higher (27.0 patients with adverse events per 100 patient years). The most common drug-related adverse events were upper respiratory tract infection and nasopharyngitis.

Study P011

In Part 1 of Study P011, the proportion of patients with one or more adverse events was comparable between 2 of the 4 treatment groups (55.1% in the placebo group and 54.0% in the etanercept group) and numerically lower in the tildrakizumab groups (44.3% in the tildrakizumab 100 mg group and 49.4% in the tildrakizumab 200 mg group). In the General Disorders and Administration Site Conditions SOC, the incidence of adverse events in the etanercept group was numerically greater mainly due to a difference in incidence rates for the specific adverse event of injection site erythema. In the Nervous System Disorders SOC, the incidence of adverse events in the placebo group was numerically lower that the incidence observed in the tildrakizumab 100 mg, tildrakizumab 200 mg and etanercept groups (4.5%, 7.8%, 10.2%, and 8.6%, respectively) with headache being the most common adverse event reported in this SOC (3.8%, 4.9%, 4.8%, 4,8%). During Part 2, the proportions of patients with one or more adverse events were similar and numerically lower for patients in the tildrakizumab treatment groups (47.4% in the tildrakizumab 100 mg group and 44.7% in the tildrakizumab 200 mg group) than the etanercept group (56.7%). In Part 3 the overall incidences of adverse events by SOC were similar in the tildrakizumab 100 mg (54.6%) and tildrakizumab 200 mg (56.8%) groups. The exposure adjusted incidence rates of patients with adverse events and drug-related adverse events by SOC during the base study were higher in the placebo and etanercept groups compared to tildrakizumab groups. Drug-related adverse events were reported most frequently for the General Disorders and Administration Site Conditions SOC (40.4, 6.4, 8.4, and 40.4 patients with adverse events per 100 patient years in the placebo, 100 mg, 200 mg, and etanercept groups, respectively) mainly due to a difference in incidence rates for the specific adverse events of injection site erythema and injection site reaction. Adverse events were reported most frequently for the Infections and Infestations SOC and the most common adverse event was nasopharyngitis.

Phase 2b/3 Trials - Placebo-controlled Safety Pool

This safety pool makes comparisons between tildrakizumab and placebo over the placebo-controlled period (16 weeks for P05495 and 12 weeks for P010 and P011). Data are pooled across trials and treatment groups and the presentation of treatment arms. Etanercept 50 mg is presented for P011 only.

One or more AEs was reported in 339 patients (47.9%) receiving tildrakizumab 200 mg, 340 patients (48.2%) receiving tildrakizumab 100 mg, 191 patients (53.8%) receiving placebo, and 169 patients

(54.0%) receiving etanercept. The incidence of drug-related AEs was similar for patients receiving tildrakizumab 200 mg (14.0%), tildrakizumab 100 mg (14.8%), and placebo (13.2%), and was higher in patients receiving etanercept (29.4%). General disorders and administration site conditions were more frequent with etanercept (20.8%) than with placebo (8.5%), tildrakizumab 200 mg (6.8%) or tildrakizumab 100 mg (8.7%), primarily due to a higher incidence of the specific AEs of injection site erythema, injection site reaction, injection site pain, and injection site swelling, and for Skin and subcutaneous tissue disorders, which were more frequent with placebo (11.8%) than with tildrakizumab 200 mg (6.2%), tildrakizumab 100 mg (5.7%) or etanercept (5.4%), primarily due to a higher incidence of the specific AEs of pruritus and psoriasis. The most frequently reported SOC was Infections and infestations. The incidence of AEs in this SOC was similar across treatment groups.

Drug Related Adverse Events

In the placebo-controlled safety pool, the incidence of drug-related AEs was comparable for the tildrakizumab 200 mg group (99 patients, 14.0%) and the tildrakizumab 100 mg group (104 patients, 14.8%) compared with the placebo group (47 patients, 13.2%) and was higher in the etanercept group (92 patients, 29.4%) compared with the other groups. The incidence of drug-related AEs was generally low across groups for the individual SOCs and specific AEs. Drug-related AEs were most frequent in the General disorders and administration site conditions where the incidence was comparable for tildrakizumab 200 mg, 100 mg and placebo (4.1%, 4.7% and 4.5%, respectively) and higher for etanercept (18.2%) and Infections and infestations SOCs where the incidence was generally comparable for tildrakizumab 200 mg, 100 mg and placebo (5.9%, 5.4% and 4.8%, respectively) and higher for etanercept (9.3%). Nasopharyngitis and headache were the most frequent drug-related AEs across treatment groups.

Table 34: Subjects with Drug-Related Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) Phase 2 and 3: Placebo-Controlled Safety Pool

	Placebo		MK-3222 100mg		MK-3222 200mg		MK-3222 100 / 200 mg		Etanercept 50mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	355		705		708		1,413		313	
with one or more drug-related adverse events	47	(13.2)	104	(14.8)	99	(14.0)	203	(14.4)	92	(29.4)
with no drug-related adverse events	308	(86.8)	601	(85.2)	609	(86.0)	1,210	(85.6)	221	(70.6)
Gastrointestinal disorders	**1**	**(0.3)**	**14**	**(2.0)**	**10**	**(1.4)**	**24**	**(1.7)**	**5**	**(1.6)**
Diarrhoea	0	(0.0)	7	(1.0)	3	(0.4)	10	(0.7)	3	(1.0)
General disorders and administration site conditions	**16**	**(4.5)**	**33**	**(4.7)**	**29**	**(4.1)**	**62**	**(4.4)**	**57**	**(18.2)**
Fatigue	4	(1.1)	9	(1.3)	2	(0.3)	11	(0.8)	2	(0.6)
Injection site erythema	1	(0.3)	3	(0.4)	3	(0.4)	6	(0.4)	26	(8.3)
Injection site haematoma	1	(0.3)	2	(0.3)	5	(0.7)	7	(0.5)	3	(1.0)
Injection site pain	3	(0.8)	10	(1.4)	6	(0.8)	16	(1.1)	10	(3.2)
Injection site pruritus	0	(0.0)	1	(0.1)	3	(0.4)	4	(0.3)	4	(1.3)
Injection site reaction	1	(0.3)	2	(0.3)	2	(0.3)	4	(0.3)	14	(4.5)
Injection site swelling	2	(0.6)	1	(0.1)	3	(0.4)	4	(0.3)	7	(2.2)
Infections and infestations	**17**	**(4.8)**	**38**	**(5.4)**	**42**	**(5.9)**	**80**	**(5.7)**	**29**	**(9.3)**
Gastroenteritis	1	(0.3)	1	(0.1)	1	(0.1)	2	(0.1)	3	(1.0)
Nasopharyngitis	6	(1.7)	22	(3.1)	16	(2.3)	38	(2.7)	15	(4.8)
Investigations	**3**	**(0.8)**	**11**	**(1.6)**	**4**	**(0.6)**	**15**	**(1.1)**	**2**	**(0.6)**
Musculoskeletal and connective tissue disorders	**5**	**(1.4)**	**5**	**(0.7)**	**6**	**(0.8)**	**11**	**(0.8)**	**1**	**(0.3)**
Nervous system disorders	**3**	**(0.8)**	**12**	**(1.7)**	**13**	**(1.8)**	**25**	**(1.8)**	**11**	**(3.5)**
Dizziness	0	(0.0)	1	(0.1)	2	(0.3)	3	(0.2)	4	(1.3)
Headache	1	(0.3)	9	(1.3)	8	(1.1)	17	(1.2)	5	(1.6)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(1.0)**
Respiratory, thoracic and mediastinal disorders	**4**	**(1.1)**	**5**	**(0.7)**	**6**	**(0.8)**	**11**	**(0.8)**	**6**	**(1.9)**
Skin and subcutaneous tissue disorders	**4**	**(1.1)**	**13**	**(1.8)**	**17**	**(2.4)**	**30**	**(2.1)**	**10**	**(3.2)**
Pruritus	1	(0.3)	1	(0.1)	7	(1.0)	8	(0.6)	7	(2.2)
Vascular disorders	**4**	**(1.1)**	**2**	**(0.3)**	**2**	**(0.3)**	**4**	**(0.3)**	**1**	**(0.3)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Phase 2b/3 Trials - Base Period Safety Pool

This safety pool supports the exposure-adjusted summary of AEs for the base period. It includes pooled data for the Phase 2 and Phase 3 base periods (52 weeks for P05495 and P011, and 64 weeks for P010) across trials and treatment groups and the presentation of treatment arms is as follows: tildrakizumab 200 mg, tildrakizumab 100 mg, continuous exposure tildrakizumab 100 mg, continuous exposure tildrakizumab 200 mg, placebo, tildrakizumab 100/200 mg (combining patients who receive tildrakizumab 100 mg or tildrakizumab 200 mg) and continuous exposure tildrakizumab 100/200 mg (combining patients who receive tildrakizumab 100 mg or tildrakizumab 200 mg throughout the base period). “Continuous exposure” defines patients who received the same dose throughout the base period without re-randomization to a different dose.

After adjustment for duration of exposure, the AE incidence rate per 100 subject-years was lower for patients receiving tildrakizumab 200 mg (79.34) and tildrakizumab 100 mg (77.03) compared with patients receiving placebo (153.52) or etanercept (148.61). The Adverse Event rate per 100 subject-years was the highest in the Infections and infestations SOC across all treatment groups, but was lower for the tildrakizumab 200 mg (52.64) and tildrakizumab 100 mg (48.88) groups than for the placebo (79.50) and etanercept (86.04) groups. Nasopharyngitis was the most common individual AE within the Infections and infestations SOC for all treatment groups. The Musculoskeletal and connective tissue disorders SOC had the next highest AE rate per 100 subject-years across treatment groups with 18.30 in the tildrakizumab 200 mg group, 18.33 in the tildrakizumab 100 mg group, 20.56 in the placebo group, and 28.68 in the etanercept group. The most common individual AEs in this SOC were back pain and arthralgia. The following most frequent SOC was Skin and subcutaneous tissue disorders which had AE rate per 100 subject-years across treatment groups of 13.13 in the tildrakizumab 200 mg group, 13.92 in the tildrakizumab 100 mg group, 31.53 in the placebo group, and 28.03 in the etanercept group. Pruritus was the most common individual AE within the Skin and subcutaneous tissue disorders SOC across treatment groups.

Drug-related Adverse Events

Across treatment groups, the exposure-adjusted AE rate per 100 subject-years for drug-related events was highest in the Infections and infestations SOC with 12.12 in the tildrakizumab 100 mg group, 15.61 in the tildrakizumab 200 mg group, 18.73 in the placebo group and 29.33 in the etanercept group. The most common individual adverse event across groups was Nasopharyngitis with an exposure-adjusted rate per 100 subject-years of 5.01, 6.46, 3.20, and 13.69, respectively.

Table 35: Subjects with Drug-Related Adverse Events (Occurring in >= 1 Subjects per 100 Subject Years in One or More Treatment Groups) Exposure Adjusted (Based on 20-Week Follow-up) Phase 2 and 3: Base Period Safety Pool All Subjects as Treated

	Placebo		MK-3222 100 mg		MK-3222 200 mg		MK-3222 100/200 mg		Etanercept 50 mg		Continuous exposure MK-3222 100 mg		Continuous exposure MK-3222 200 mg		Continuous exposure MK-3222 100 / 200 mg[a]	
	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)
Subjects in population	588		1083		1041		1911		313		381		363		933	
with one or more drug-related adverse events	83	37.92	233	23.34	234	25.19	451	23.40	112	73.00	110	22.35	106	22.27	274	22.73
with no drug-related adverse events	505	230.74	850	85.14	807	86.88	1460	75.76	201	131.01	271	55.06	257	53.98	659	54.66
Blood and lymphatic system disorders	**0**	**0.00**	**7**	**0.70**	**3**	**0.32**	**10**	**0.52**	**2**	**1.30**	**6**	**1.22**	**2**	**0.42**	**8**	**0.66**
Gastrointestinal disorders	**2**	**0.91**	**25**	**2.50**	**20**	**2.15**	**45**	**2.34**	**8**	**5.21**	**13**	**2.64**	**9**	**1.89**	**32**	**2.65**
Diarrhoea	0	0.00	9	0.90	7	0.75	16	0.83	4	2.61	4	0.81	4	0.84	10	0.83
Nausea	0	0.00	5	0.50	4	0.43	9	0.47	2	1.30	2	0.41	3	0.63	7	0.58
General disorders and administration site conditions	**19**	**8.68**	**51**	**5.11**	**47**	**5.06**	**98**	**5.09**	**62**	**40.41**	**32**	**6.50**	**25**	**5.25**	**72**	**5.97**
Fatigue	4	1.83	11	1.10	6	0.65	17	0.88	2	1.30	4	0.81	4	0.84	10	0.83
Injection site bruising	0	0.00	4	0.40	3	0.32	7	0.36	2	1.30	3	0.61	1	0.21	6	0.50
Injection site erythema	2	0.91	7	0.70	6	0.65	13	0.67	27	17.60	5	1.02	3	0.63	9	0.75
Injection site haematoma	1	0.46	5	0.50	7	0.75	12	0.62	3	1.96	5	1.02	3	0.63	12	1.00
Injection site pain	4	1.83	12	1.20	11	1.18	23	1.19	10	6.52	8	1.63	7	1.47	18	1.49
Injection site pruritus	0	0.00	3	0.30	6	0.65	9	0.47	5	3.26	2	0.41	4	0.84	7	0.58
Injection site reaction	2	0.91	4	0.40	5	0.54	9	0.47	17	11.08	3	0.61	2	0.42	6	0.50
Injection site swelling	3	1.37	2	0.20	3	0.32	5	0.26	7	4.56	2	0.41	1	0.21	4	0.33
Hepatobiliary disorders	**1**	**0.46**	**2**	**0.20**	**2**	**0.22**	**3**	**0.16**	**2**	**1.30**	**1**	**0.20**	**1**	**0.21**	**3**	**0.25**
Infections and infestations	**41**	**18.73**	**121**	**12.12**	**145**	**15.61**	**260**	**13.49**	**45**	**29.33**	**55**	**11.17**	**70**	**14.70**	**159**	**13.19**
Bronchitis	0	0.00	3	0.30	11	1.18	14	0.73	2	1.30	2	0.41	9	1.89	11	0.91
Gastroenteritis	2	0.91	4	0.40	4	0.43	8	0.42	4	2.61	1	0.20	3	0.63	4	0.33
Gingivitis	0	0.00	1	0.10	0	0.00	1	0.05	2	1.30	1	0.20	0	0.00	1	0.08
Influenza	4	1.83	7	0.70	4	0.43	11	0.57	1	0.65	1	0.20	3	0.63	7	0.58
Nasopharyngitis	7	3.20	50	5.01	60	6.46	107	5.55	21	13.69	27	5.49	30	6.30	76	6.30
Oral herpes	1	0.46	4	0.40	4	0.43	8	0.42	2	1.30	1	0.20	2	0.42	4	0.33
Pharyngitis	1	0.46	6	0.60	3	0.32	9	0.47	2	1.30	2	0.41	1	0.21	5	0.41
Rhinitis	0	0.00	4	0.40	5	0.54	9	0.47	3	1.96	2	0.41	4	0.84	7	0.58
Sinusitis	3	1.37	9	0.90	11	1.18	20	1.04	1	0.65	7	1.42	6	1.26	14	1.16
Tooth infection	0	0.00	2	0.20	2	0.22	4	0.21	4	2.61	1	0.20	2	0.42	3	0.25
Upper respiratory tract infection	12	5.48	14	1.40	31	3.34	45	2.34	3	1.96	6	1.22	18	3.78	26	2.16
Urinary tract infection	1	0.46	3	0.30	6	0.65	9	0.47	1	0.65	2	0.41	5	1.05	8	0.66
Investigations	**5**	**2.28**	**22**	**2.20**	**13**	**1.40**	**35**	**1.82**	**4**	**2.61**	**8**	**1.63**	**8**	**1.68**	**19**	**1.58**
Alanine aminotransferase increased	2	0.91	6	0.60	3	0.32	9	0.47	2	1.30	4	0.81	2	0.42	6	0.50
Musculoskeletal and connective tissue disorders	**6**	**2.74**	**16**	**1.60**	**16**	**1.72**	**32**	**1.66**	**3**	**1.96**	**7**	**1.42**	**8**	**1.68**	**18**	**1.49**
Arthralgia	2	0.91	5	0.50	7	0.75	12	0.62	2	1.30	2	0.41	3	0.63	6	0.50
Nervous system disorders	**4**	**1.83**	**23**	**2.30**	**21**	**2.26**	**44**	**2.28**	**15**	**9.78**	**11**	**2.23**	**9**	**1.89**	**26**	**2.16**
Dizziness	1	0.46	3	0.30	4	0.43	7	0.36	4	2.61	1	0.20	3	0.63	5	0.41
Headache	1	0.46	12	1.20	15	1.61	27	1.40	6	3.91	9	1.83	4	0.84	17	1.41
Psychiatric disorders	**0**	**0.00**	**4**	**0.40**	**3**	**0.32**	**7**	**0.36**	**3**	**1.96**	**4**	**0.81**	**0**	**0.00**	**4**	**0.33**
Renal and urinary disorders	**0**	**0.00**	**8**	**0.80**	**4**	**0.43**	**12**	**0.62**	**0**	**0.00**	**6**	**1.22**	**1**	**0.21**	**8**	**0.66**
Respiratory, thoracic and mediastinal disorders	**7**	**3.20**	**12**	**1.20**	**15**	**1.61**	**27**	**1.40**	**7**	**4.56**	**7**	**1.42**	**10**	**2.10**	**22**	**1.82**
Cough	1	0.46	4	0.40	4	0.43	8	0.42	3	1.96	3	0.61	3	0.63	6	0.50
Oropharyngeal pain	3	1.37	5	0.50	5	0.54	10	0.52	0	0.00	2	0.41	3	0.63	9	0.75
Skin and subcutaneous tissue disorders	**14**	**6.40**	**27**	**2.70**	**39**	**4.20**	**66**	**3.42**	**13**	**8.47**	**12**	**2.44**	**21**	**4.41**	**44**	**3.65**
Acne	0	0.00	1	0.10	1	0.11	2	0.10	2	1.30	1	0.20	1	0.21	2	0.17
Erythema	0	0.00	1	0.10	5	0.54	6	0.31	2	1.30	1	0.20	2	0.42	4	0.33
Hyperhidrosis	0	0.00	3	0.30	2	0.22	5	0.26	2	1.30	2	0.41	0	0.00	2	0.17
Pruritus	1	0.46	3	0.30	13	1.40	16	0.83	8	5.21	1	0.20	6	1.26	11	0.91
Psoriasis	7	3.20	3	0.30	4	0.43	7	0.36	1	0.65	2	0.41	1	0.21	5	0.41
Vascular disorders	**4**	**1.83**	**8**	**0.80**	**8**	**0.86**	**16**	**0.83**	**4**	**2.61**	**5**	**1.02**	**5**	**1.05**	**10**	**0.83**
Haematoma	1	0.46	1	0.10	0	0.00	1	0.05	2	1.30	1	0.20	0	0.00	1	0.08
Hypertension	1	0.46	4	0.40	4	0.43	8	0.42	2	1.30	3	0.61	3	0.63	6	0.50

† m is the number of subjects with event per 100-subject-year.

[a] Includes subjects who stayed on one of the 100 mg or 200 mg throughout the whole Base period.

A system organ class or adverse event appears on this report only if it occurred in >=1 subjects per 100 subject years in one or more treatment groups of Placebo, MK-3222 100mg, MK-3222 200mg, and Etanercept 50mg.

Source: [ISS: analysis - ADSL; ADAE]

In the base period safety pool, the rate of AEs leading to discontinuation per 100 subject-years was low overall and similar for the tildrakizumab 200 mg (2.15), the tildrakizumab 100 mg (2.20) and placebo (2.28) groups, but was higher for the etanercept group (5.87) compared with the other groups.

The applicant also presents a Phase 3 Extension Safety Pool. This Pool includes the Phase 3 extension data up to the targeted cut-off dates of 12-Jun-2016 (P010) and 21-Jun-2016 (P011). Tildrakizumab 100 mg and tildrakizumab 200 mg were pooled across trials. Additionally, updated safety data up to 27-May-2017 are provided.

Updated Phase 3 extension safety pool

By the cut-off date of 27 May 2017, cumulatively 954 subjects reported one or more adverse events compared to 797 subjects in April 2016. Compared with the 2016 data there was an increase in number of subjects who discontinued study medication due to an adverse event across both treatment arms (from 13 to 22 subjects in the 100 mg arm and from 3 subjects to 13 subjects in the 200 mg arm).

Therefore, there was an increase in the number of subjects experiencing adverse events when cumulative data up to May 2017 was compared with the earlier cut-off in April 2016. This increase in numbers of AEs is expected when data are observed along time (cumulative data).

Table 36: Subjects With Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) Phase 3: Extension Safety Pool All Subjects as Treated

	Cut-off date 15-April-2016				Cut-off date: 27-May-2017				Cumulative			
	MK-3222 100mg		MK-3222 200mg		MK-3222 100mg		MK-3222 200mg		MK-3222 100mg		MK-3222 200mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	621		616		574		586		620		616	
with one or more adverse events	399	(64.3)	398	(64.6)	328	(57.1)	352	(60.1)	474	(76.5)	480	(77.9)
with no adverse events	222	(35.7)	218	(35.4)	246	(42.9)	234	(39.9)	146	(23.5)	136	(22.1)
Blood and lymphatic system disorders	8	(1.3)	7	(1.1)	7	(1.2)	7	(1.2)	15	(2.4)	14	(2.3)
Cardiac disorders	14	(2.3)	10	(1.6)	13	(2.3)	20	(3.4)	26	(4.2)	25	(4.1)
Eye disorders	8	(1.3)	13	(2.1)	4	(0.7)	11	(1.9)	16	(2.6)	21	(3.4)
Gastrointestinal disorders	59	(9.5)	64	(10.4)	48	(8.4)	67	(11.4)	95	(15.3)	104	(16.9)
Diarrhoea	16	(2.6)	9	(1.5)	11	(1.9)	10	(1.7)	26	(4.2)	18	(2.9)
General disorders and administration site conditions	36	(5.8)	31	(5.0)	20	(3.5)	27	(4.6)	47	(7.6)	48	(7.8)
Hepatobiliary disorders	7	(1.1)	4	(0.6)	7	(1.2)	8	(1.4)	14	(2.3)	13	(2.1)
Infections and infestations	260	(41.9)	265	(43.0)	178	(31.0)	199	(34.0)	327	(52.7)	330	(53.6)
Bronchitis	14	(2.3)	19	(3.1)	7	(1.2)	10	(1.7)	24	(3.9)	26	(4.2)
Gastroenteritis	13	(2.1)	16	(2.6)	9	(1.6)	10	(1.7)	23	(3.7)	24	(3.9)
Influenza	18	(2.9)	22	(3.6)	14	(2.4)	18	(3.1)	28	(4.5)	38	(6.2)
Nasopharyngitis	8	(1.3)	4	(0.6)	5	(0.9)	8	(1.4)	15	(2.4)	11	(1.8)
Sinusitis	16	(2.6)	14	(2.3)	11	(1.9)	10	(1.7)	23	(3.7)	16	(2.6)
Upper respiratory tract infection	26	(4.2)	43	(7.0)	32	(5.6)	37	(6.3)	46	(7.4)	64	(10.4)

At the cut-off date of 27 May 2017, the incidence of subjects with one or more drug-related AEs increased in both treatment arms (from 14.8% to 17.9% in the 100 mg arm and from 16.6% to 19.0% in the 200 mg arm). Overall, the incidence of drug-related AEs was generally low across both treatment arms for the specific SOCs and AEs. At the cut-off date of 27 May 2017, drug-related AEs were most frequent in the Infections and infestations SOC.

Table 37: Adverse Event summary Phase 3: extension safety pool all subjects as treated (cut-off date 27 May 2017)

	Tildrakizumab 100mg		Tildrakizumab 200mg		Total	
	N	(%)	N	(%)	N	(%)
Subjects in population	620		616		1,236	
with one or more adverse events	474	(76.5)	480	(77.9)	954	(77.2)
with no adverse event	146	(23.5)	136	(22.1)	282	(22.8)
with drug-related† adverse events	111	(17.9)	117	(19.0)	228	(18.4)
with serious adverse events	89	(14.4)	75	(12.2)	164	(13.3)
with serious drug-related adverse events	15	(2.4)	6	(1.0)	21	(1.7)
who died	3	(0.5)	2	(0.3)	5	(0.4)
discontinued‡ due to an adverse event	22	(3.5)	13	(2.1)	35	(2.8)
discontinued due to a drug-related adverse event	10	(1.6)	2	(0.3)	12	(1.0)
discontinued due to a serious adverse event	14	(2.3)	10	(1.6)	24	(1.9)
discontinued due to a serious drug-related adverse event	7	(1.1)	1	(0.2)	8	(0.6)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Source: Table 2.7.4- 19

Drug-related adverse events

At the cut-off date of 27 May 2017, the incidence of subjects with one or more drug-related AEs increased in both treatment arms (from 14.8% to 17.9% in the 100 mg arm and from 16.6% to 19.0% in the 200 mg arm). Overall, the incidence of drug-related AEs was generally low across both treatment arms for the specific SOCs and AEs. At the cut-off date of 27 May 2017, drug-related AEs were most frequent in the Infections and infestations SOC. A similar pattern observed at the cut-off date of 15 April 2016.

Adverse Events of Special Interest

Tier 1 Adverse Events

Safety parameters or adverse events of special interest that were identified a priori constituted the "Tier 1" safety endpoints. These endpoints were based on tildrakizumab mechanism of action and specific risks in the target subject population. The Tier 1 safety endpoints included: severe infections, malignancies, non-melanoma skin cancer, melanoma skin cancer, MACE, drug-related hypersensitivity.

Study P010

After adjustment for exposure, the incidence rates of severe infections and confirmed extended MACE events were numerically greater in the tildrakizumab 200 mg group compared with the placebo and tildrakizumab 100 mg groups. No adverse events of melanoma skin cancer were reported during the base study.

Study P011

After adjustment for exposure, the incidence rates of specific Tier 1 adverse events during the base study were similar in the placebo, tildrakizumab 100 mg, tildrakizumab 200 mg, and etanercept groups.

Tier 2 Adverse Events

The following pre-specified safety/tolerability endpoints were considered Tier 2 regardless of the number of patients in any treatment group: adverse events, drug-related adverse events, serious adverse events, discontinuation due to adverse events, discontinuation due to drug-related adverse events, specific adverse events, deaths, adverse events associated with ADA, confirmed MACE and confirmed thrombotic/embolic/ischemic CV adverse events.

All AE summary measures were treated as Tier 2 (ie, subjects with one or more AEs, drug-related AEs, SAEs, serious drug-related AEs, deaths, discontinuations due to AEs, discontinuations due to SAEs, discontinuations due to drug-related AEs, and discontinuations due to drug-related SAEs). In addition, confirmed MACE and confirmed thrombotic/embolic/ischemic cardiovascular events were also considered Tier 2 AEs. In general the overview given by the pooled Tier 2 data is useful. In the extension safety pool the general incidence of any adverse event was comparable between doses. AEs relating to individual categories such as discontinuations, SAEs and MACE report higher incidence in the 100mg dose which is favourable for the proposed 200mg dose.

Study P010

After adjustment for exposure, the incidence rates of serious adverse events, discontinuation due to adverse events, discontinuation due to drug-related adverse events, and confirmed CV adverse events were numerically greater in the tildrakizumab 200 mg group compared with the placebo and tildrakizumab 100 mg groups. In contrast, higher incidences of patients with adverse events, drug-related adverse events, and adverse events not including worsening of psoriasis were observed in the placebo group, as compared with the tildrakizumab 100 mg and 200 mg groups.

Study P011

After adjustment for exposure, the incidence rates of patients with Tier 2 adverse events during the base study were generally similar in the tildrakizumab 100 mg and tildrakizumab 200 mg groups. In the etanercept and placebo groups, higher incidences of patients with adverse events, drug-related adverse events, serious adverse events, who discontinued due to an adverse event, and adverse events not including worsening of psoriasis were observed.

General disorders and administration site conditions were more frequent with etanercept (20.8%) than with placebo (8.5%), tildrakizumab 200 mg (6.8%) or tildrakizumab 100 mg (8.7%), due to a higher incidence of the specific AEs of injection site erythema, injection site reaction, injection site pain, and injection site swelling, and for Skin and subcutaneous tissue disorders, which were more frequent with placebo (11.8%) than with tildrakizumab 200 mg (6.2%), tildrakizumab 100 mg (5.7%) or etanercept (5.4%), due to a higher incidence of the specific AEs of pruritus and psoriasis.

The Applicant confirmed that during clinical development there were no adverse events reported for erythrodermic psoriasis, inverse psoriasis, palmoplantar psoriasis or worsening or exacerbation of psoriasis during the Phase 2 or Phase 3 studies. The only psoriasis-type adverse events reported under the SOC Skin and Subcutaneous Tissue Disorders were psoriasis, pustular psoriasis and guttate psoriasis. There were few subjects who experienced adverse events related to psoriatic disease, and discontinuation of tildrakizumab treatment did not lead to rebound.

SIB

Safety information pertaining to suicidal ideation and behaviour (SIB) across the Tildrakizumab development program was reviewed for tildrakizumab in 2015 when the presumptive signal for SIB in the brodalumab development program became public knowledge. This review identified no reports describing a completed suicide, and 2 reports (one from a Phase one trial, one from a Phase 3 trial) describing non-fatal SIB events, across the entire tildrakizumab development program (described below). In studies P003, P010 and P011, for the base period safety pool, the incidence of suicide attempt was reported in 1/1039 (0.1%, CI 0.0-0.5) patients.

The applicant included SIB in the RMP. However, new cases of SIB including 2 cases of completed suicide were reported in the updated long term extension safety pool. One case of completed suicide was reported for a subject with a medical history of anxiety, psoriasis, attention deficit/hyperactivity disorder, who died due to an SAE of completed suicide (self-inflicted gunshot in the head) on Day 1227. No prior history of suicide attempts or family history of suicide was reported by the subject's family. Relevant concomitant medications included alprazolam and atomoxetine. No other adverse events were reported during the study.

A second case of completed suicide for a subject with a medical history of psoriasis and former tobacco user was reported to have died due to the SAE of completed suicide (jumping of roof) on Day 1306. Relevant concomitant medications included methylphenidate hydrochloride, amphetamine aspartate (+) amphetamine sulfate (+) dextroamphetamine saccharate (+) dextroamphetamine sulfate, and pregabalin. This reported case has been adjudicated post-hoc, as “completed suicide”. Additionally all reported cases of completed suicide have been implemented and the SIB event rate has been recalculated as requested by the CHMP/PRAC. The incidence rate of completed suicide per 100 subject-years for tildrakizumab is 0.05 and an association between psoriasis and SIB has been thoroughly described in several studies for the overall psoriasis population. No causal association between the treatment with tildrakizumab and the completed suicides has been established. The reported cases of completed suicide are considered not related to the treatment with tildrakizumab although this can never be excluded completely. This is therefore considered as a potential risk in the safety concerns.

Table 38: Incidence of Suicidal Ideation and Behaviour adverse events. Base Safety Pool and Extension Period (cut-off: 27th May 2017)

	Base Safety pool		Base Safety pool and Extension period cumulative up 27th May 2017	
Time	64w (P-010) 56w (P-011)		108w	
Patients	1994		1994	
Patient-Years	2059		4130,2	
	n	**Incidence 100 subject-year**	**n**	**Incidence 100 subject-year**
Suicidal Ideation	2	0,10	5	0,12
Suicidal Attempt	1	0,05	1	0,02
Complete Suicide*	0	0,00	2*	0,05
Total SIB	3	0,15	8	0,19

Table 39: SIB Event rates in the tildrakizumab phase 2/3 program (updated)

Treatment	N	Exposure patient-years*	Completed suicides N	Suicide Behaviors/ attempts N	Suicides / 100,000 PY	Attempt/ 100,000 PY	Suicides + Attempts/ 100,000 PY	Suicidal ideation N	Ideation / 100,000 PY
Tildrakizumab	1994	4130.24	2**	1	48.4	24.2	72.6	5	121.1
Placebo		218.9	0	0	0	0	0	0	0
Etanercept		155.5	0	0	0	0	0	0	0

PY: patients year

* Cut off date for exposure: (SUR) 27th May 2017; N: number of cases; PY: patients-years

**One out of these 2 completed suicide events occurred after the cut-off date of May 27th 2017 (in June 2017)

Sources: SIB Adjudication; Table 2.7.4: 1 from section 2.7.4; Table 24_6 from the Statistical Report. D120 update (amendment 1).

Patient Age / sex Dose and Period	Adverse event	Relevant Medical history for SIB	Relevant Prior/Concomitant medication	Comment
24 y-o male 400mg (single dose) Phase 1	Suicidal ideation	Psoriasis, Multiple psychosocial stressors (expatriate status, severe financial hardship due to unemployment, compulsive gambling and substantial gambling debt)	Unkown	Japanese patient admitted to the hospital for 1 day for psychiatric assessment and observation. Considered as a missing person by his housemates who found a suicide note. He was discharged from hospital under the care of his family with the expressed intention of returning to Japan. No medications were administered. The SAE

Patient Age / sex Dose and Period	Adverse event	Relevant Medical history for SIB	Relevant Prior/Concomitant medication	Comment
				was considered resolved.
43y-o / male 200mg Base period	Suicide attempt	Psoriasis, insomnia, schizophrenia, dystonia. (The subject reported concern regarding the condition of his dystonia as the inciting cause of the suicide attempt)	Alprazolam, aripiprazole, baclofen, biperiden, brotizolam, clonazepam, diazepam, eperisone, etizolam, flunitrazepam, olanzapine, quetiapine, risperidone, triazolam, and zolpidem	On Day 12, the subject was hospitalized after attempted suicide by cutting his abdominal wall with a knife. The investigator has attributed the event to the patient's concern about his concomitant dystonia, and the patient's underlying condition of schizophrenia.
24 y-o / male 100mg Extension	Suicidal ideation	Depression was known since the age of 17 (in 2008) Psoriasis and arthritis. Hepatic steatosis, hypertension, psychosocial stressors: unemployed after losing job multiple times.	Sertraline, amlodipine, lisinopril, hydrochlorothiazide, bisoprolol, and doxazosin	On Day 922, the subject experienced an episode of depression without psychotic symptoms. No action was taken the study medication; he continued into the next trial segment uneventfully several months following hospital discharge.
47 y-o / male 200mg Extension	Completed suicide	Psoriasis, anxiety, attention deficit/ hyperactivity disorder, diverticulitis, lymphadenopathy	Alprazolam Atomoxetine	The subject committed suicide on Day 1227. The subject died of a self-inflicted gunshot in the head. Atomoxetine a selective norepinephrine reuptake inhibitor and non-stimulant treatment option for ADHD, has also been associated with increased SIB risk. Alprazolam, a benzodiazepine indicated for the treatment of anxiety and panic disorders, includes a precaution regarding the risk of suicide
40 y-o / female 100mg Extension	Suicidal ideation	Psoriasis, ovarian cyst, hot flashes, menstrual cramps, mild hematuria, arthritis shoulders, pruritus, constipation, bilateral tubal ligation and congentital nevus left inguinal fold	Naproxen, Difenhidramina Laxatives	On Day 1071 the subject experienced suicidal thoughts. The subject discontinued the trial on day 1269 due to withdrawal by subject. No more data is available
50 y-o / female 200/ 100mg Extension	Suicidal ideation	Psoriasis, Adenoviral conjunctivitis, perioral dermatitis, hysterectomy, periodontosis	Pantoprazole	On day 1116 the subject experienced suicidal thoughts, the patient continued with tildrakizumab and recovered on day 1123.
45 y-o male 200/100mg Extension	Completed suicide	Psoriasis, tabaco user. Loss of concentration, and facial nerve damage. Financial issues and patient had expressed concern about "the CIA following the subject" in an email prior to committing suicide. Possible low self-esteem	Methylphenidate, amphetamine aspartate, amphetamine sulphate, dextroamphetamine saccharate dextroamphetamine sulfate, and pregabalin.	The subject committed suicide on Day 1306. Potential paranoic syndrome; he had expressed concern about CIA was following him. Pregabalin, a member of an antiepileptic drug class have an acknowledged association with an increased risk of SIB. The patient's concurrent use of methylphenidate (MPH) and mixed amphetamine salts, two stimulant medications having a known association with psychotic symptoms, are also considered potentially contributory

As described in the response to D180LoI the applicant accepted to include serious psychiatric events as an outcome of interest in the proposed registry study, which is considered adequate. For these reasons the implementation of a warning statement in the SmPC is considered not necessary.

The PRAC/CHMP requested also addition of irritable bowel disease as potential risk based on current safety profile and knowledge of products impacting the IL23/IL17 pathway.

ADR

The applicant revised the ADRs listed in section 4.8 upon request and included Headache, Upper respiratory tract infections and Nasopharyngitis in a revised proposal for Section 4.8 of the SmPC.

Serious adverse events and deaths

Study P010

In Part 1 of Study P010, serious adverse were reported for 1 (0.6%) patient in the placebo group, 5 (1.6%) patients in the tildrakizumab 100 mg group and 8 (2.6%) patients in the tildrakizumab 200 mg group of which 3 serious adverse events resulted in discontinuation of study medication during Part 1. Serious adverse events in Part 2 were reported for 7 (1.9%) patients in the tildrakizumab 100 mg group and 8 (2.2%) patients in the tildrakizumab 200 mg group. Four serious adverse events resulted in discontinuation of study medication: One squamous cell carcinoma of skin (tildrakizumab 100 mg), one bone tuberculosis (tildrakizumab 200 mg), one case of psoriasis (tildrakizumab 200 mg) and one patient with pancreatic carcinoma (tildrakizumab 200 mg). During Part 3 serious adverse events were reported for 14 (4.4%) patients in the tildrakizumab 100 mg group and 21 (5.8%) patients in the tildrakizumab 200 mg group.

The incidence rates of patients with drug-related serious adverse events during all parts of the study were similar in the placebo, tildrakizumab 100 mg and tildrakizumab 200 mg groups (1.2, 0, and 1.0 patients with adverse events per 100 patient years, respectively).

Table 40 Subjects with Serious Drug-Related Serious Adverse Events P010 Base Study: Adjusted for Exposure

	Placebo†			MK-3222 100 mg‡			MK-3222 200 mg‡		
	n	M§	Expo. Adj.‖	n	M§	Expo. Adj.‖	n	M§	Expo. Adj.‖
Subjects in population††	387	8904		383	20268		399	21795	
With one or more serious drug-related adverse events	2		(1.2)	0			4		(1.0)
With no serious drug-related adverse events	385		(225.6)	383		(98.6)	395		(94.6)
Infections and infestations	**1**		**(0.6)**	**0**			**3**		**(0.7)**
Bone tuberculosis	0			0			1		(0.2)
Cellulitis	1		(0.6)	0			1		(0.2)
Epiglottitis	0			0			1		(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**		**(0.6)**	**0**			**0**		
Benign biliary neoplasm	1		(0.6)	0			0		
Skin and subcutaneous tissue disorders	**0**			**0**			**1**		**(0.2)**
Psoriasis	0			0			1		(0.2)

†Includes placebo subjects who took at least one dose of placebo in Part 1 or during placebo period in Part 3.
‡Includes subjects who received MK-3222 100 mg or MK-3222 200 mg anytime during the study.
§M = person-time (person-weeks) exposure to treatment (start of treatment to end of treatment).
‖Exposure adjustment is calculated as (52.17857143 weeks * n/M)*100.
††Includes subjects who took at least one dose of Part 1 or Part 2 or Part 3 study medication based on the treatment actually received. Subjects are counted only once in the overall category. The same subject may appear in different categories. Events were counted in each treatment group based on the treatment the subject actually received when the event occurred.
MedDRA Version: Merck T2-MedDRA.

Study P011

Serious adverse events during Part 1 were reported 2.6% of patients in the placebo group, 1.3% in the tildrakizumab 100 mg group, 1.9% in the tildrakizumab 200 mg group and 2.2% in the etanercept group. The incidences of overall serious adverse events by SOC were similar in the tildrakizumab 100 mg, tildrakizumab 200 mg, etanercept, and placebo groups. Serious adverse events during Part 2 were reported for 2.8% of the patients in the tildrakizumab 100 mg group, 2.2% in the tildrakizumab 200 mg group and 4.8% in the etanercept group. Serious adverse events during Part 3 were reported for 4.6% in the tildrakizumab 100 mg group and 3.7% patients in the tildrakizumab 200 mg group.

0.5% of the patients in the tildrakizumab 100 mg group (1 bladder transitional cell carcinoma and 1 thyroid cancer) and 0.3% in the tildrakizumab 200 mg group (1 breast cancer) reported a serious drug-related adverse event during Part 3.

After adjustment for exposure, the incidence rate of patients with serious adverse events during the base study was higher in the placebo and etanercept groups (11.5 and 13 patients with serious adverse events per 100 patient years, respectively) compared with the tildrakizumab 100 mg and tildrakizumab 200 mg groups (6.6 and 6.2 patients with serious adverse events per 100 patient year, respectively).

Drug-Related Serious Adverse Events

The incidence rate of patients with serious drug-related adverse events during the base study was comparable between the tildrakizumab 100 mg group and the tildrakizumab 200 mg group (0.4 and 0.7 patients with serious drug-related adverse events per 100 patient years, respectively). The incidence rate in the etanercept group was 3.3 patients with serious drug-related adverse events per 100 patient years.

Table 41: Subjects With Serious Drug-Related Adverse Events P011 Base Study: Adjusted for Exposure

	Placebo[†]			MK-3222 100 mg[‡]			MK-3222 200 mg[‡]			Etanercept		
	n	M[§]	Expo. Adj.[‖]	n	M[§]	Expo. Adj.[‖]	n	M[§]	Expo. Adj.[‖]	n	M[§]	Expo. Adj.[‖]
Subjects in Population[††]	156	1808		487	23763		527	21780		313	8005	
With one or more serious drug-related adverse events	0			2		(0.4)	3		(0.7)	5		(3.3)
With no serious drug-related adverse events	156		(450.2)	485		(106.5)	524		(125.5)	308		(200.8)
Hepatobiliary disorders	**0**			**0**			**0**			**1**		**(0.7)**
Bile duct stone	0			0			0			1		(0.7)
Infections and infestations	**0**			**0**			**2**		**(0.5)**	**2**		**(1.3)**
Herpes zoster	0			0			1		(0.2)	1		(0.7)
Urosepsis	0			0			0			1		(0.7)
Wound infection	0			0			1		(0.2)	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**			**2**		**(0.4)**	**1**		**(0.2)**	**1**		**(0.7)**
Bladder transitional cell carcinoma	0			1		(0.2)	0			0		
Breast cancer	0			0			1		(0.2)	1		(0.7)
Thyroid cancer	0			1		(0.2)	0			0		
Nervous system disorders	**0**			**0**			**0**			**1**		**(0.7)**
Headache	0			0			0			1		(0.7)

[†] Includes Placebo subjects who took at least one dose of Placebo in Part 1.
[‡] Includes subjects who received MK-3222 100 mg or MK-3222 200 mg anytime during the study.
[§] M = person-time (person-weeks) exposure to treatment (start of treatment to end of treatment).
[‖] Exposure adjustment is calculated as (52.17857143 weeks * n/M.)*100.
[††] Includes subjects who took at least one dose of Part 1 or Part 2 or Part 3 study medication based on the treatment actually received. Subjects are counted only once in the overall category. The same subject may appear in different categories.
MedDRA Version: Merck T2-MedDRA.

Phase 2b and Phase 3 Base Period Safety Pool

The rate of SAEs per 100 patient-years in the Phase 2b and Phase 3 Base Period Safety Pool was similar for the tildrakizumab 200 mg group at 7.21 and the tildrakizumab 100 mg group at 5.81

compared with the placebo group at 6.40, but was higher for the etanercept group at 13.04. Overall the SAE rate was low across treatment groups for the specific SOCs and AEs. No SOC had an SAE rate of more than 1.61 patients with events per 100 patient-years with the exception of the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC. Within the Neoplasms SOC, the highest incidence rate per 100 patient-years was noted for the etanercept group with 3.26 compared to placebo with 1.37, tildrakizumab 100mg with 1.50 and tildrakizumab 200 mg with 1.08. The rate for the continuous tildrakizumab groups was even lower.

The rate of drug-related SAEs per 100 patient-years was low for the tildrakizumab 200 mg group (0.97), the tildrakizumab 100 mg group (0.30) and the placebo group (0.91), compared with the etanercept group (3.26). The highest drug-related SAE rate across groups was noted for the Infections and infestations SOC.

Table 42: Subjects with Serious and Drug-Related Adverse Events Exposure Adjusted (Based on 20-Week Follow-up) Phase 2 and 3: Base Period Safety Pool (All Subjects as Treated)

	Placebo		MK-3222 100 mg		MK-3222 200 mg		MK-3222 100/200 mg		Etanercept 50 mg		Continuous exposure MK-3222 100 mg		Continuous exposure MK-3222 200 mg		Continuous exposure MK-3222 100 / 200 mg*	
	n	(mT)	n	(mT)	n	(mT)	n	(mT)	n	(mT)	n	(mT)	n	(mT)	n	(mT)
Subjects in population	588		1083		1041		1911		313		381		363		933	
with one or more serious drug-related adverse events	2	0.91	3	0.30	9	0.97	12	0.62	5	3.26	1	0.20	1	0.21	5	0.41
with no serious drug-related adverse events	586	267.75	1080	108.18	1032	111.10	1899	98.54	308	200.76	380	77.20	362	76.04	928	76.98
Hepatobiliary disorders	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**1**	**0.65**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**
Bile duct stone	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00
Infections and infestations	**1**	**0.46**	**1**	**0.10**	**6**	**0.65**	**7**	**0.36**	**2**	**1.30**	**0**	**0.00**	**1**	**0.21**	**4**	**0.33**
Bone tuberculosis	0	0.00	0	0.00	1	0.11	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00
Cellulitis	1	0.46	0	0.00	2	0.22	2	0.10	0	0.00	0	0.00	1	0.21	2	0.17
Epiglottitis	0	0.00	1	0.10	1	0.11	2	0.10	0	0.00	0	0.00	0	0.00	1	0.08
Herpes zoster	0	0.00	0	0.00	1	0.11	1	0.05	1	0.65	0	0.00	0	0.00	0	0.00
Urosepsis	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00
Wound infection	0	0.00	0	0.00	1	0.11	1	0.05	0	0.00	0	0.00	0	0.00	1	0.08
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**0.46**	**2**	**0.20**	**1**	**0.11**	**3**	**0.16**	**1**	**0.65**	**1**	**0.20**	**0**	**0.00**	**1**	**0.08**
Benign biliary neoplasm	1	0.46	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bladder transitional cell carcinoma	0	0.00	1	0.10	0	0.00	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00
Breast cancer	0	0.00	0	0.00	1	0.11	1	0.05	1	0.65	0	0.00	0	0.00	0	0.00
Thyroid cancer	0	0.00	1	0.10	0	0.00	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08
Nervous system disorders	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**1**	**0.65**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**
Headache	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00
Skin and subcutaneous tissue disorders	**0**	**0.00**	**0**	**0.00**	**1**	**0.11**	**1**	**0.05**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**
Psoriasis	0	0.00	0	0.00	1	0.11	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00
Vascular disorders	**0**	**0.00**	**0**	**0.00**	**1**	**0.11**	**1**	**0.05**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**	**0**	**0.00**
Lymphoedema	0	0.00	0	0.00	1	0.11	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00

T m is the number of subjects with event per 100-subject-year.
* Includes subjects who stayed on one of the 100 mg or 200 mg through out the whole Base period.
Source: [ISS: analysis - ADSL; ADAE]

The proportion of subjects with serious adverse events was low in the tildrakizumab group and similar to that for the placebo group and most SAEs reported in subjects exposed to tildrakizumab were single events.

In the base period safety pool, the SAE rate per 100 subject-years was similar for the tildrakizumab 200 mg group at 7.21 and the tildrakizumab 100 mg group at 5.81 compared with the placebo group at 6.40, but was higher for the etanercept group at 13.04. With the exception of the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC, no SOC had an SAE rate of more than 1.61 subjects with events per 100 subject-years. The drug-related SAE rate per 100 subject-years across groups for the tildrakizumab 200 mg group was (0.97), the tildrakizumab 100 mg group (0.30) and the placebo group (0.91), compared with the etanercept group (3.26). The highest drug-related SAE rate across groups was noted for the Infections and infestations SOC. No SOC or specific drug-related SAE had an exposure-adjusted AE incidence rate of more than 1.30 subjects per 100 subject-years.

In general with respect to all Tier 1 adverse events, data from the pooled placebo-controlled periods did not demonstrate a significant higher rate of AEs for subjects treated with tildrakizumab compared with subjects treated with placebo. In the base period safety pool, AE incidence with exposure to

tildrakizumab 100mg and 200mg is comparable to exposure to continuous exposure to tildrakizumab 100/200mg. In addition AEs are similar for both the 100mg and 200mg tildrakizumab doses in the extension safety pool. Although infection is a theoretical risk for tildrakizumab based on its immune-modulating mechanism of action, data from the pooled safety data did not demonstrate a significant higher rate of infection. One event of TB which was deemed by the investigator as related to tildrakizumab was reported. Section 4.3 and 4.4 of the SmPC contain information regarding this identified risk: "Clinically important active infection (e.g. active tuberculosis, see section 4.4)."

A low incidence of malignancy (including non-melanoma and melanoma skin cancer) was reported in general throughout the safety data pools. However considering that numerically the majority of observed malignant diseases were observed in tildrakizumab treated patients, this raises concern, and the possible association with tildrakizumab treatment needs to be further investigated. Patients with psoriasis may have an increased risk of non-melanoma skin cancers, in particular squamous cell carcinoma associated with psoralen-PUVA-therapy. Also the performed clinical trials are short considering the length of tumor induction, thus no conclusions concerning the possible aetiology of the observed malignant diseases can be made. The Applicant should submit the most recent follow up results regarding malignancies.
Considering the overall increased risk for cancer development in psoriasis, the observed cases of malignant diseases and experience from other biological medical products, malignancies is considered an important potential risk in the RMP.
The rate of CV events for tildrakizumab 100 mg group (0.40) is comparable to the placebo group (0.46) and lower than the etanercept group (0.65). This is also consistent with other biologics with the same indication. The rate of CV events for tildrakizumab 200 mg group (0.86) is low however higher than all other comparisons, the applicant is asked to further clarify and discuss biological plausibility.

In the Phase III Extension Trials SAEs occurred in 7.4% of the 100mg group and 5% of the 200mg group. No SOC had a frequency of SAEs >1.3% in any treatment group. Most SAEs occurred in only 1 or 2 subjects, with the exception of cholelithiasis, osteoarthritis and psoriatic arthropathy, which occurred in 3 subjects (all in the 100 mg dose group). No further details have been provided. Drug-related SAEs reported in the tildrakizumab 200 mg group (2 SAEs in 2 subjects, 0.3%) were infectious colitis and pneumonia. Drug-related SAEs reported in the tildrakizumab 100 mg group (12 SAEs in 11 subjects, 1.8%) were thyrotoxic crisis, gastritis erosive, mesenteric artery thrombosis, appendicitis, gastroenteritis, staphylococcal infection, breast cancer, diffuse large B-cell lymphoma, cerebral infarction, cerebrovascular accident, loss of consciousness, and hypertensive crisis. The incidence of drug-related SAEs reported in the Phase III base period safety pool was low incidence with no trend for any specific safety signal.

Updated Phase 3 extension safety pool

At cut-off date 27 May 2017 an overall increase in the incidence of SAEs was reported in patients in the gastrointestinal disorders, infectious diseases, neoplasm and nervous disorders SOC. There were no new SAEs reported in the surgical and medical procedures SOC.

10 patients discontinued in the 200 mg arm due to one or more SAE. Four of the 10 patients discontinued due to different SAEs of carcinoma the neoplasm SOC. Two patients discontinued due to asphyxia and chronic obstructive pulmonary disease in the Respiratory, thoracic and mediastinal disorders SOC and 4 patients discontinued due to SAEs of coronary artery disease, inappropriate antidiuretic hormone secretion, hepatitis E and transient ischaemic attack. In the 100 mg arm, 9 patients discontinued due to 1 or more SAE. 7 patients discontinued due to different SAEs of carcinoma in the neoplasm SOC. One patient discontinued due to an SAE of diverticulitis and another subject discontinued due to an SAE of psoriatic arthropathy. One extra death was reported in each treatment arm at the cut-off date of 27 May 2017.

Drug-related SAEs reported in the 100 mg arm (13 SAEs in 10 patients) were angina pectoris, gastritis erosive, mesenteric artery thrombosis, diverticulitis, gastroenteritis, pneumonia, diffuse large B-cell, metastatic carcinoma of the bladder, non-hodgkin's lymphoma, carotid artery stenosis, cerebral infarction, loss of consciousness and hypertensive crisis. Drug-related SAEs reported in the 200 mg arm (7 SAEs in 6 patients) were gastric polyps, large intestine polyp, appendicitis, infectious colitis, peritonitis, pneumonia mycoplasmal, and chronic obstructive pulmonary disease.

Deaths

Phase 1 Trials

There were no deaths reported in the 6 Phase 1 trials involving tildrakizumab (P05661, P05776, P06306, P05382, P009 and P05839).

Phase 2b/3 Trials

A total of 7 patients experienced fatal AEs during the base trial periods:

1. Aneurysm (tildrakizumab 200 mg)
2. Unknown cause (tildrakizumab 100 mg)
3. cardiomyopathy alcoholic and steatohepatitis (tildrakizumab 100 mg)
4. acute myeloid leukaemia (tildrakizumab 100 mg)
5. respiratory arrest (tildrakizumab 100 mg)
6. myocardial infarction (tildrakizumab 100 mg)
7. sepsis (etanercept in Part 1, switched to tildrakizumab 200 mg in Part 3)

None of the 7 deaths in patients receiving tildrakizumab was causally-related to tildrakizumab. All patients had related risk-factors in their medical history. Two of the deaths occurred in patients with a history of alcohol abuse, which is strongly considered to be a likely contributory factor in the aetiology of the fatal events. Two occurred in patients who were diagnosed with malignancies. 3 deaths occurred in patients with known cardiovascular risk factors who experienced events that were adjudicated as fatal MACE events.

The new cumulative listing with a cut-off date of 27 May 2017 now includes a further 2 cases of death, in addition to the 7 already reported: one patient due to intracranial haemorrhage and another who completed suicide. Finally, the coding of the AE of one patient was changed from the initial code of accidental death (at cut-off date 15 April 2016) to asphyxia (at cut-off date 27 May 2017). One additional case of completed suicide was reported during the long term extension period.

A second case of completed suicide was reported during the long term extension. However this case was not adjudicated by the blinded adjudication committee at the time the responses were submitted. (See also above Adverse Events of Special Interest - SIB)

Laboratory findings

Phase I- Healthy subjects (P05661, P05775, P06306)

There are no integrated analyses for laboratory safety data for the Phase 1 program. All descriptive summaries of laboratory safety data, were included in the individual CSRs. There were no clinically meaningful trends for changes in laboratory values within each trial.

Phase IIB/III

In the integrated analysis of the Phase 2b/3 trials, it was reported that there were no meaningful differences in the results and flow of the laboratory values across the treatment groups. In the tabular listing of adverse events only few and single events from adverse laboratory values are seen. Events of clinical interest (ECI) for reports of elevated AST or ALT lab value that was ≥3 × the ULN and an elevated total bilirubin lab value that was ≥2 × ULN and, at the same time, an ALP lab value that was <2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing, reported as a non-serious ECI.

Change from Baseline in laboratory values over time is summarized for the base period safety pool in subjects with continuous exposure to tildrakizumab from week 4 to Week 52.

Urinalysis was performed at the site via dipstick test. If the dipstick was positive (i.e., trace or above), a sample was sent to the central laboratory for microscopic examination Laboratory assessments were performed at various time-points during the Phase 2b/3 trials. Since the 3 trials had different visit schedules, for the purpose of comparison of results across time, only the trial visits common across the Phase 2b and Phase 3 trials were summarized. Common time-points for measurement of laboratory values across the Phase 2b (P05495) and Phase 3 (P010 and P011) trials during the base period were Weeks 0, 4, 12/16 (Week 12 [P010 and P011] and Week 16 [P05495]), 28, and 52.

The Applicant provided, as requested, separate analyses for the placebo-controlled pool, the base period pool, and data from the extension period up to the most recent cut-off date of 27 May 2017. During 220 weeks of exposure only sporadic changes and low numbers of higher grades of toxicity occurred in all groups. No dose relationship and no safety concern can be identified.

Table 43: Summary of Laboratory Assessment over Time - Haematology Phase 2 and 3: Base Period Safety Pool

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Platelet (10[3]/microL)								
Week 4	continuous exposure MK-3222 100 mg	246	242.3 (57.3)	[102.0, 438.0]	238.5 (58.9)	[110.0, 443.0]	-3.8 (34.4)	[-167.0, 136.0]
	continuous exposure MK-3222 200 mg	202	243.7 (53.8)	[118.0, 391.0]	239.9 (51.2)	[121.0, 397.0]	-3.8 (27.3)	[-132.0, 112.0]
	continuous exposure MK-3222 100 / 200 mg	614	240.9 (55.2)	[102.0, 438.0]	236.8 (54.7)	[110.0, 443.0]	-4.1 (31.0)	[-167.0, 136.0]
Week 12/16	continuous exposure MK-3222 100 mg	245	241.9 (57.4)	[102.0, 438.0]	232.3 (53.2)	[107.0, 419.0]	-9.6 (29.4)	[-122.0, 98.0]
	continuous exposure MK-3222 200 mg	208	240.3 (56.3)	[36.0, 391.0]	232.3 (53.5)	[53.0, 427.0]	-7.9 (29.4)	[-113.0, 98.0]
	continuous exposure MK-3222 100 / 200 mg	619	239.5 (56.5)	[36.0, 438.0]	231.2 (52.7)	[53.0, 427.0]	-8.3 (29.2)	[-122.0, 98.0]
Week 28	continuous exposure MK-3222 100 mg	241	242.4 (57.2)	[102.0, 438.0]	236.7 (53.8)	[99.0, 387.0]	-5.7 (32.6)	[-209.0, 75.0]
	continuous exposure MK-3222 200 mg	206	240.7 (56.8)	[36.0, 391.0]	238.0 (54.8)	[56.0, 440.0]	-2.7 (26.8)	[-82.0, 91.0]
	continuous exposure MK-3222 100 / 200 mg	613	240.0 (56.6)	[36.0, 438.0]	235.7 (53.4)	[56.0, 440.0]	-4.3 (30.2)	[-209.0, 119.0]
Week 52	continuous exposure MK-3222 100 mg	246	242.4 (57.4)	[102.0, 438.0]	238.3 (54.4)	[113.0, 390.0]	-4.0 (37.0)	[-181.0, 115.0]
	continuous exposure MK-3222 200 mg	202	240.1 (56.7)	[36.0, 391.0]	233.3 (52.1)	[94.0, 430.0]	-6.8 (36.9)	[-166.0, 129.0]
	continuous exposure MK-3222 100 / 200 mg	615	239.6 (56.5)	[36.0, 438.0]	234.7 (52.8)	[94.0, 430.0]	-5.0 (35.2)	[-181.0, 129.0]

Table 44: Shifts in laboratory values for neutrophils and platelets relative to the reference range from baseline to worst – Phase 2 and 3: Base period safety pool – Continuous exposure – all subjects as treated

		Number (%) of Subjects								
		Baseline Low			Baseline Normal			Baseline High		
Treatment	n	Low	Normal	High	Low	Normal	High	Low	Normal	High
Neutrophils (10[3]/µL) (MAX)										
continuous exposure tildrakizumab 100mg	250	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	217 (86.8)	18 (7.2)	0 (0.0)	7 (2.8)	7 (2.8)
continuous exposure tildrakizumab 200 mg	209	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	188 (90.0)	10 (4.8)	0 (0.0)	5 (2.4)	5 (2.4)
continuous exposure tildrakizumab 100 / 200 mg	625	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	548 (87.7)	40 (6.4)	0(0.0)	18 (2.9)	16 (2.6)
Neutrophils (10[3]/µL) (MIN)										
continuous exposure tildrakizumab 100 mg	250	0 (0.0)	1 (0.4)	0 (0.0)	7 (2.8)	228 (91.2)	0 (0.0)	0 (0.0)	12 (4.8)	2 (0.8)
continuous exposure tildrakizumab 200 mg	209	0 (0.0)	1 (0.5)	0 (0.0)	4 (1.9)	194 (92.8)	0 (0.0)	0 (0.0)	10 (4.8)	0 (0.0)
continuous exposure tildrakizumab 100 / 200 mg	625	0 (0.0)	3 (0.5)	0 (0.0)	16 (2.6)	572 (91.5)	0 (0.0)	0 (0.0)	31 (5.0)	3 (0.5)
Platelet (10[3]/µL) (MAX)										
continuous exposure tildrakizumab 100 mg	245	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	233 (95.1)	7 (2.9)	0 (0.0)	2 (0.8)	1 (0.4)
continuous exposure tildrakizumab 200 mg	208	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)	199 (95.7)	3 (1.4)	0 (0.0)	1 (0.5)	2 (1.0
continuous exposure tildrakizumab 100 / 200 mg	618	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.3)	593 (96.0)	12 (1.9)	0 (0.0)	3 (0.5)	4 (0.6)
Platelet (10[3]/µL) (MIN)										
continuous exposure tildrakizumab 100 mg	245	1 (0.4)	0 (0.0)	0 (0.0)	5 (2.0)	236 (96.3)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)
continuous exposure tildrakizumab 200 mg	208	2 (1.0)	0 (0.0)	0 (0.0)	4 (1.9)	199 (95.7)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)
continuous exposure tildrakizumab 100 / 200 mg	618	4 (0.6)	0 (0.0)	0 (0.0)	10 (1.6)	597 (96.6)	0 (0.0)	0 (0.0)	7 (1.1)	0 (0.0)

For each laboratory test, only subjects with baseline and at least one post-baseline value and reference range are included. The worst value can either be the minimum (min) or the maximum (max) in the reporting period.
References ranges: Neutrophil count - 1.7-7.9 10^9/L; platelet count -125-375 10^9/L.
Low = below reference range; Normal = within reference range; High = above reference range.
Source: Table 6 from Analyses of clinical studies D121.

The applicant presented further analyses, shift tables for changes from baseline in platelet count and neutrophils to below or above the respective reference ranges following treatment, as requested in D120 LoQ. For most patients no change in the laboratory values is seen. Numbers of patients with Grade 3 neutropenia are low and no dose trend could be determined.

Safety in special populations

Subgroup analyses results for the Phase 2b/3 placebo-controlled safety pool were presented in the dossier. The AE profile for tildrakizumab versus placebo and etanercept was evaluated for the following subgroups:

- Body weight (≤90 kg, >90kg)
- Prior exposure to biologic therapy for psoriasis (Yes, No)
- Age (<65 years, ≥65 years)
- Gender (Female, Male)
- Race (White, Asian, Other Races)
- Region (North America, Europe, Rest of World)
- Failure of at least one traditional systemic therapy (methotrexate, cyclosporine, phototherapy) (Yes, No)
- Tumor necrosis factor (TNF) antagonist response among subjects previously treated for psoriasis (Yes, No)
- Psoriatic arthritis (Yes, No)
- Disease duration category (<15 median years, ≥15 median years)

- Baseline BSA involvement category (<30%, ≥30%)
- Baseline PASI category (<20, ≥20)
- Baseline PGA category (≤3, ≥4)
- ADA status (Positive, Negative)

In general, the AE profile was comparable for tildrakizumab, placebo, and etanercept across the subgroups of ≥65 years and gender. Drug-related AEs which were reported with a higher frequency in the etanercept group than in the tildrakizumab and placebo groups in a majority of subgroup categories. Consistent with these findings, the Exposure-Response (E-R) evaluation conducted using all subjects treated with tildrakizumab or placebo from Part 1 of the Phase 3 trials (P010 and P011) concluded that no E-R relationship could be observed between exposure and safety across doses of 100 mg and 200 mg.

The incidence of AEs, drug-related (per investigator) AEs, SAEs, and discontinuations due to AEs was comparable for subjects with body weight ≤90 kg compared to those with body weight >90 kg. This is consistent with findings of the exposure-response analysis, in which an assessment of safety by dose and body weight subgroup was performed. No differential safety profile was determined for subjects with low body weight (≤90 kg) compared with those with higher body weights (>90 kg). When comparing placebo, 100 mg, and 200 mg in all subjects in Part 1 of P010 and P011, no specific differences in AEs) were observed. Similarly, when comparing 100 mg with 200 mg integrated across Part 1 and Part 2, no important differences were seen in AEs (infections/infestations, severe infections/infestations, URTI and nasopharyngitis, basal/squamous cell carcinoma, melanoma, myocardial infarction/ischemia, cardiac failure, drug hypersensitivity), with Infections and infestations being the most frequent SOC. Thus, it was found that treating subjects, in either weight category, with a 200 mg SC regimen does not increase the safety risk.

The incidence of AEs, drug-related (per investigator) AEs, SAEs, and discontinuations due to AEs was comparable for subjects with or without prior exposure to biologic therapy for psoriasis. This is consistent with findings of the population PK analysis. Prior treatment of psoriasis with a biological agent was tested as potential covariate in the population PK analysis, but did not have a statistically significant influence on tildrakizumab exposure. In the exposure-response and longitudinal PK-(pharmacodynamic) PD models, PASI 75 response rates were similar in subjects regardless of prior treatment of psoriasis with a biological agent. The population PK model was used to simulate tildrakizumab PK in subjects with and without prior treatment of psoriasis with a biological agent using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting area under the curve at steady state (AUCSS) geometric mean ratio (GMRs) [90% CI] for subjects with/without prior treatment of psoriasis with a biological agent receiving 100 mg and 200 mg SC were 0.90 [0.85, 0.95] and 0.89 [0.85, 0.84], respectively. Thus, the effect of prior treatment of psoriasis with a biological agent on tildrakizumab PK was not considered to be clinically meaningful and no dose adjustment was deemed to be warranted.

Elderly

Patients aged 18 years or older were included in the clinical trial programme. A total of 175 patient's ≥65 years old (155 patients aged between 65 and 75 and 20 patients ≥75 years old) were included in the base period safety pool. The overall safety profile in patient ≥ 65 years old and ≥75 years old were comparable with younger populations (< 65 years old and < 75 years old respectively). There was a mild increase in the frequency of some adverse events reported in ≥ 65 years old such as hypertension, COPD, atrial fibrillation, basal cell or squamous cell carcinoma of skin, which is expected for elderly population.

Table 45:- elderly population- repartition across age groups

MedDRA Terms	Age <65 N=1294 n (%)	Age 65-74 N=104 n (%)	Age 75-84 N=15 n (%)	Age 85+ N=0 n (%)
Total AEs	621 (47.99)	50 (48.08)	8 (53.33)	0
Serious AEs – Total	21 (1.62)	5 (4.81)	0	0
- Fatal	2 (0.15)	0	0	0
- Hospitalization/prolong existing hospitalization	16 (1.24)	5 (4.81)	0	0
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	2 (0.15)	1 (0.96)	0	0
AE leading to drop-out	5 (0.39)	2 (1.92)	0	0
Psychiatric disorders	27 (2.09)	0	0	0
Nervous system disorders	101 (7.81)	3 (2.88)	0	0
Accidents and injuries	38 (2.94)	3 (2.88)	1 (6.67)	0
Cardiac disorders	10 (0.77)	3 (2.88)	0	0
Vascular disorders	19 (1.47)	4 (3.85)	1 (6.67)	0
Cerebrovascular disorders	1 (0.08)	0	0	0
Infections and infestations	292 (22.57)	22 (21.15)	1 (6.67)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	19 (1.47)	2 (1.92)	1 (6.67)	0
<other AE appearing more frequently in older patients>	[See discussion below]			

Source: Table 21.4 from Post-hoc Analyses D120

The occurrence of total AEs is similar in all age groups. However, it has to be noted that the numbers of patients over 75 years is small.

Pregnant or breast feeding women

There is inadequate data in pregnancy and lactation in the clinical development programme to form a conclusion of safety. This special population is represented accordingly in the SmPC.

Female patients who were pregnant or lactating were excluded from enrolment in the clinical trials. A total of 13 pregnancies occurred across the whole clinical development programme. There were 2 pregnancies reported in the Phase 1 trials (P05661 and P05839), and 11 pregnancies reported in the Phase 2b/3 trials, including 2 patients in P05495, 5 patients in P010 and 4 patients in P011.

Pregnancy outcomes included 6 deliveries of healthy term infants, 6 cases of fetal loss and in one case outcome is not available to date. In relation to the fetal loss there were 4 elective abortions and 2 spontaneous abortions occurring at week 4 and week 8 of the pregnancy in patients who were smokers, one of whom also had a pregnancy history that included an ectopic pregnancy and another miscarriage in addition to 2 full term live births.

In the updated safety extension pool at the cut-off date of 27 May 2017, there were 4 new cases of pregnancy. In the tildrakizumab 200 mg arm, two subjects had live births by C-section and one subject had a vaginal live birth. In the tildrakizumab 100 mg arm, one subject had a live birth by C-section.

Patients with hepatic impairment

No formal trials with tildrakizumab on patients with hepatic impairment have been conducted. Patients with significant organ dysfunction (such as significant hepatic dysfunction) were excluded from the clinical trials. Among patients receiving tildrakizumab during the base period, there were 90 patients with medical history of hepatic impairment in the Phase 2b/3 trials.

The AEs observed in these patients were comparable with AEs observed with the overall population. No additional safety concern was identified in this patient group.

Patients with renal impairment

No formal trials with tildrakizumab on patients with renal impairment have been conducted. Patients with significant organ dysfunction (such as significant renal dysfunction) were excluded from the clinical trials.

When the renal function is assessed based on the Glomerular Filtration Renal estimation (eGFR) at baseline, there were 1328 patients with normal renal function, 609 patients with mild renal impairment, 56 patients with moderate renal impairment and 1 patient with severe renal impairment. There were no patients with renal failure. No additional safety concern was identified on these populations. No adverse events were reported in the only patient with severe renal impairment (eGFR: < 30).

Table 46: Clinical trial exposure by special populations in patients with psoriasis (Phase 2 and 3)

Special populations in patients with psoriasis	Number of patients (N=1994)	Patient Years
Pregnant women[a]	7	4.1
Lactating women	NA	NA
Hepatic impairment[b]	90	99.0
Sub populations with genetic polymorphism[c]	NA	NA
Immuno-compromised[d]	8	6.7
Patients with history of infectious diseases[e]	286	309.6
Renal impairment[f]		
No renal impairment	1328	1367.7
Mild renal impairment	609	630.9
Moderate renal impairment	56	60.4
Severe renal impairment	1	0.1
Renal failure	0	0
Cardiac impairment[g]	463	466.6
Psoriasis severity[h]		
PASI > 10 (moderate and severe)	1986	2050.8
PASI <= 10 (mild)	6	6.7
Patients with prior exp. to bio. therapy for psoriasis	361	364.0
Patients with prior conventional systemic therapy	799	827.5

Source: Table 7: RMP.

NA=Not Applicable.

[a] Pregnant women were excluded from studies at screening. However, some women became pregnant during the studies.

Discontinuation reason due to pregnancy was used to identify these women.

[b] Hepatic impairment based on medical history of hepatobiliary disorders.

[c] Only if any genetic polymorphisms study has been performed.

[d] Immunocompromised patients: Patients with concomitant use of any of the drugs included in the following ATCs: L01, or L03A, or L04A.

[e] History of infectious diseases based on medical history of infections and infestations.

[f] Renal function categorized based on baseline eGFR: normal when eGFR≥90, mild when 60≤eGFR<90, moderate when 30≤eGFR<60, severe when 15≤eGFR<30 and renal failure when eGFR<15.

[g] Cardiac impairment base on medical history of cardiac disorders

[h] Moderate and severe psoriasis based on baseline PASI score.

For duration, each priming dose is counted as 4 weeks of exposure and each subsequent dose is counted as 12 weeks.

Exposure in patient years -- multiply exposure in weeks by 7 to get exposure in days and divide by 365.25.

Base Period for P003 is Week 0 to Week 52, for P010 is Week 0 to Week 64, for P011 is Week 0 to Week 52.

Immunological events

Across healthy subject trials (P05561, P05776 and P06306) and psoriasis trials (P05382 and P009), AEs were pooled and categorized by ADA status. Treatment emergent ADA positive subjects in the integrated AE tables were compared to negative and inconclusive subjects (combined).

Treatment emergent anti-tildrakizumab antibodies showed no discernible effects on safety (eg, AEs, including ISRs) in the Phase 1 trials.

Across healthy subject trials (P05561, P05776 and P06306), of the 103 subjects treated with tildrakizumab, 101 subjects were considered ADA evaluable and included in the analysis. While there was no trend for the presence of ADAs to impact AEs, the number of subjects with treatment emergent ADA (10, 9.9%) is small and no relationship between ADA and ISR could be found.

In the immunogenicity evaluation in the Phase 2b/3 trials, the ADA-evaluable population included individuals with at least one ADA sample after dosing with tildrakizumab; therefore, subjects treated with placebo or etanercept during Part 1 of the trials were not part of the ADA-evaluable population in the placebo controlled safety pool.

In this analysis of the Phase 2b and Phase 3 placebo controlled safety pool, Treatment-Emergent Positive (TE-POS) subjects were compared with negative and inconclusive subjects (combined). The TE-POS subject category contains both subjects who had at least one sample test positive for neutralizing antibodies (NAb-POS) and subjects who were negative for NAb (NAb-NEG).

The overall incidence of antibodies against tildrakizumab was low (4.1% through 12-16 weeks and 8.2% through 52-64 weeks.).

Table 47: ADA Incidence in Subjects treated with 100 mg or 200 mg Tildrakizumab through Week 16 (Phase 2b) and Week 12 (Phase 3)

Trial	Dose (mg)†	Total dosed MK-3222†	Total Evaluable†‡	Negative§	Inconclusive§‖	Non-treatment-emergent Positive§		Treatment-emergent Positive§	
		N	N	N (%)	N (%)	ADA positive N (%)	NAb positive N (%)	ADA positive N (%)	NAb positive N (%)
P05495¶	100	89	89	80 (89.9%)	1 (1.1%)	4 (4.5%)	0	4 (4.5%)	0
P010#	100	309	308	267 (86.7%)	12 (3.9%)	16 (5.2%)	5 (1.6%)	13 (4.2%)	2 (0.6%)
P011#	100	307	303	256 (84.5%)	16 (5.3%)	18 (5.9%)	0	13 (4.3%)	2 (0.7%)
Summary	100	705	700	603 (86.1%)	29 (4.1%)	38 (5.4%)	5 (0.7%)	30 (4.3%)	4 (0.6%)
P05495¶	200	86	86	69 (80.2%)	5 (5.8%)	5 (5.8%)	0	7 (8.15)	0
P010#	200	308	305	161 (52.8%)	108 (35.4%)	21 (6.9%)	3 (1.0%)	15 (4.9%)	4 (1.3%)
P011#	200	314	309	144 (46.6%)	142 (46.0%)	16 (5.2%)	3 (1.0%)	7 (2.3%)	0
Summary	200	708	700	374 (53.4%)	255 (36.4%)	42 (6.0%)	6 (0.9%)	29 (4.1%)	4 (0.6%)
100/200 mg Summary		1413	1400	977 (69.8%)	284 (20.3%)	80 (5.7%)	11 (0.8%)	59 (4.2%)	8 0.6%)

†: Includes subjects treated with listed dose amount of MK-3222 (100 mg or 200 mg) in Part 1.
‡: Includes subjects with at least one ADA sample available after treatment with MK-3222.
§ Denominator is total number of evaluable subjects.
¶In P05495, Part 1 ended at Week 16; # In P010 and P011, Part 1 ended at Week 12.
MK-3222 = tildrakizumab: TE-POS = treatment emergent positive; Non-TE-POS = Non-treatment emergent positive
[P05495ada02.xpt], [P010adada03.xpt], [P011adada05.xpt],[Immunogenicity Report-Available on Request]

The integrated ADA data through 12-16 weeks included patients treated with 100 mg (N=700) or 200 mg (N=700) tildrakizumab. The integrated ADA incidence through 52-64 weeks was summarized for evaluable patients who were treated continuously with 100 mg (N=400) or 200 mg (N=380) in Phase 2b and Phase 3 for 52-64 weeks. For patients in Phase 2b and Phase 3 dosed with 100 mg, the proportion of TE-POS patients increased over time from 4.3% through 12-16 weeks to 6.5% through 52-64 weeks. In addition, the proportion of patients who were TE-POS and NAb-POS was 0.6% (4 of 700) through 12-16 weeks and 2.5% (10 of 400) through 52-64 weeks.

A similar proportion of patients dosed with 200 mg was TE-POS was 4.1% (29 of 700) through 12-16 weeks and 8.2% (31 of 380) through 52-64 weeks. In addition, the proportion of patients who were TE-POS and NAb-POS was 0.6% (4 of 700) through 12-16 weeks and 3.2% (12 of 380) through 52-64 weeks.

The number of treatment emergent ADA positive patients with available PASI and PGA scores was small (N=7 and N=13 for tildrakizumab 200 mg and 100 mg, respectively). Patients with treatment emergent ADAs in both dose groups showed numerically higher proportions achieving the primary endpoint at Week 12. In the tildrakizumab 200 mg group, the proportion of patients with PASI 75 response or PGA score of “clear” or “minimal” at Week 12 was higher for treatment emergent positive patients (86% and 71% for PASI and PGA, respectively) compared with negative/inconclusive patients (67% and 62%, respectively). The data suggests that ADA did not reduce the efficacy observed at Week 12. However, a large number of samples are classifies as inconclusive. The ADA assay and the large number of inconclusive samples have to be further discussed by the applicant. For more information please refer to the pharmacokinetic section (section 2.1.2).

For patients treated with 200 mg that were TE-POS NAb-POS (N=4), the percent improvement in PASI score was less (38%) relative to negative patients (76%) through Week 12. However, as this result is based on only 4 patients in the Phase 2b/3 Period, this has to be further evaluated.

Adverse Events in ADA positive patients

After adjustment for exposure, the incidence rate of patients with 1 or more specific adverse events among ADA positive patients during the base study was comparable between the tildrakizumab 100 mg and tildrakizumab 200 mg groups. No meaningful differences could be identified to the individual parts of the base study. Adverse events among ADA positive patients were reported most frequently for the Infections and Infestations SOC and the most common adverse event was nasopharyngitis.

Overall, the presence or absence of ADA does not seem to impact significantly on the rate at which adverse events are reported.

Injection site reactions (ISRs)

In protocols P05776 and P06306 (Part 1), tildrakizumab was administered as a single SC injection at doses ranging from 50 mg to 400 mg. 24% of the subjects in the tildrakizumab group and 22.2% of the subjects in the placebo group were reported to have an AE related to an ISR. With the exception of 1 event, all ISRs occurred within 2 weeks post dose and were considered drug-related by the investigators. All ISRs reported in the trials were transient and mild in severity.

All treatment emergent ISRs reported as AEs were also reviewed by subjects' anti-drug antibody (ADA) status. Of the 75 subjects treated subcutaneously with tildrakizumab, 74 subjects were considered ADA evaluable (since one or more samples were available post-tildrakizumab administration), with treatment-emergent ADAs reported in 8 (10.8%) subjects. Considering that the number of subjects who were treatment emergent ADA positive and the incidence of ISRs were small in the integrated Phase 1 healthy subject dataset (P05776 and P06306, Part 1), no relationship between ADAs and ISRs could be found.

In the Phase I patient trials (psoriasis and Crohn's disease trials) no subjects were reported to have an AE associated with an ISR.

In the Phase 2b/III placebo controlled trials ISRs were reported at a comparable incidence for tildrakizumab 100mg, 200,g and placebo 3.4, 4.0 and 2.3% respectively with a higher incidence in subjects taking etanercept (17.9%). Similar results are seen in the Phase 2b/III base period safety pools, see table excerpt below n (event per 100-subject-year).

Table 48: Phase 2b/III base period safety pools, incidence of ISRs, n(event per 100-subject-year)

With Injection Site Reactions		
Placebo	11	(5.03)
MK-3222 100 mg	35	(3.51)
MK-3222 200 mg	43	(4.63)
MK-3222 100 / 200 mg	78	(4.05)
Continuous exposure MK-3222 100 mg	22	(4.47)
Continuous exposure MK-3222 200 mg	22	(4.62)
Continuous exposure MK-3222 100 / 200 mg[e]	59	(4.89)
Etanercept 50 mg	62	(40.41)

ISRs in the Extension safety pool for tildrakizumab 100mg and 200mg respectively were reported using the definition of Tier 1 AE at an incidence of 1.0 and 1.1%.

An integrated analysis of all tildrakizumab-related hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema) reported in the Phase 1 program was performed using the definition of a Tier 1 AE

established for the Phase 2b/3 trials. Across the Phase 1 trials in both healthy subjects and subjects with psoriasis, no subject was reported to have a tildrakizumab-related hypersensitivity reaction.

In the placebo-controlled safety pool, the incidence of hypersensitivity reactions was low with tildrakizumab 200 mg (1 subject, 4.0%) and tildrakizumab 100 mg (1 subject, 4.0%) and comparable to that of placebo (1 subject, 0.3%). The incidence of subjects reporting hypersensitivity reactions receiving etanercept was 0 subjects, 0%. No important differences in AE frequency were noted between the tildrakizumab 100 mg or tildrakizumab 200 mg group and the placebo group for drug-related hypersensitivity reactions. Notably, drug-related hypersensitivity reactions for the tildrakizumab dose groups involved hypersensitivity to concomitant medications and not to tildrakizumab.

Table 49: Analysis of Subjects with Tier 1 Adverse Events Phase 2 and 3: Placebo-Controlled Safety Pool All Subjects as Treated

The incidence of ISRs was comparable, in terms of their number per 100-subject year, in the tildrakizumab 100 mg, 200 mg and placebo arms for the base study safety period, while the etanercept arm demonstrated considerably higher rates. The values for the placebo, 100 mg, 200 mg and etanercept arms were 5.03, 3.51, 4.63 and 40.41, respectively. The severity levels for all the AEs associated with ISRs ranged from mild to moderate and they were comparable between the 100 mg and 200 mg doses. No severe ISRs were recorded.

Safety related to drug-drug interactions and other interactions

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g. IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Although a role for IL-23 in the regulation of CYP450 enzymes has not been reported, the effect of tildrakizumab on CYP450 enzyme activity was evaluated in a disease-drug-drug interaction study, where all patients received a single dose of up to five cytochrome P450 probe substrates as a cocktail (midazolam, omeprazole, caffeine, dextromethorphan, warfarin + vitamin K). The results indicate that there is no clinically meaningful effect on CYP450 enzyme activity.

Discontinuation due to AES

Phase 1 Trials

Across the Phase 1 program (P05561, P05776, P06306, P05382, P009), 7 subjects were discontinued due to an AE. Three of these discontinuations occurred prior to the subjects receiving trial treatment. In addition, in the Crohn's trial, 1 subject discontinued due to pregnancy.

Phase 2b/3 Trials

The rate of Adverse Events leading to discontinuation per 100 patient-years in the Phase 2/3 Base Period Pool was similar across the treatment groups with the exception for etanercept. The rate for the tildrakizumab 200 mg was 2.15, for the tildrakizumab 100 mg 2.20 and for placebo 2.28. For the etanercept group the rate of AE´s leading to discontinuation was 5.87, which is more than double compared to the tildrakizumab 200 mg treatment group. Across the treatment groups, no SOC or specific AE leading to discontinuation had an exposure-adjusted rate of >1.3 (in the etanercept treatment group). For the tildrakizumab 200 mg or tildrakizumab 100 mg groups, no SOC had an exposure-adjusted rate of discontinuations due to AEs of >0.43 or >0.60, respectively. The most frequent SOC leading to discontinuation in the tildrakizumab 200 mg group was Infections and Infestations with 0.43 followed by Neoplasms and Nervous system disorders with 0.32 each.

2.6.1. Discussion on clinical safety

The clinical development program included evaluations of tildrakizumab across 9 completed trials: 6 Phase 1 trials - P05382 (P001), P05661 (P004), P05776 (P005), P05839 (P006), P06306 (P007), and P009. There was one Phase 2b trial - P05495 (P003) and two Phase 3 trials - P010 and P011.

A total of 1994 patients received any dose of tildrakizumab at some point during the base trial periods (42 patients received at least the 5 mg dose; 123 patients received at least the 25 mg dose; 1083 patients received at least the 100 mg dose and 1041 patients received at least the 200 mg dose). The mean duration of treatment was 53.9 weeks for tildrakizumab during the base trial periods, corresponding to an exposure of 2059.04 subject-years.

Phase 1 trials were conducted in healthy subjects (P05661, P05775, P06306), patients with moderate-to-severe psoriasis (P05382, P009) and patients with Crohn's Disease (P05389). More than 60% of participants in each study reported at least one Adverse Events. Common adverse events reported were headache with 27.2% in the healthy subjects, 17.3% in patients with psoriasis, 13% in patients with Crohn´s disease and infections with 27.2% in the healthy subjects, 14.7% in patients with psoriasis.

In the Phase 2b/3 Trials Placebo-controlled Safety Pool 47.9% patients receiving tildrakizumab 200 mg, 48.2% receiving tildrakizumab 100 mg, 53.8% receiving placebo and 54.0% receiving etanercept reported one or more AEs. The incidence of drug-related AEs was similar for the tildrakizumab 200 mg (14.0%), tildrakizumab 100 mg (14.8%), and placebo (13.2%) groups and was higher in patients receiving etanercept (29.4%). General disorders and administration site conditions were more frequent with etanercept (20.8%) than with placebo (8.5%), tildrakizumab 200 mg (6.8%) or tildrakizumab 100 mg (8.7%), which can be explained by the different dosing regimen and known side effects of etanercept. The most frequently reported SOC was Infections and infestations. The most frequently reported specific AEs as well as the most frequent drug-related AEs across treatment groups were nasopharyngitis and headache.

After adjustment for duration of exposure, the AE incidence rate per 100 subject-years in the Phase 2b/ 3 Base Period Pool was lower in the tildrakizumab 200 mg (79.34) and tildrakizumab 100 mg (77.03) groups compared with patients receiving placebo (153.52) or etanercept (148.61). The Adverse Event rate per 100 subject-years was the highest in the Infections and infestations SOC across all treatment groups, but was lower for the tildrakizumab 200 mg (52.64) and tildrakizumab 100 mg (48.88) groups than for the placebo (79.50) and etanercept (86.04) groups. Nasopharyngitis was the most common individual AE within the Infections and infestations SOC for all treatment groups. Skin and subcutaneous tissue disorders were more frequent in the placebo (31.53) group than in the

tildrakizumab 200 mg (13.13), tildrakizumab 100 mg (13.92) or etanercept (28.03) groups, due to a higher incidence of the specific AEs of pruritus and psoriasis.

The risk of SIB is unknown. All reported cases of completed suicide have been adjudicated and implemented and the SIB event rate has been recalculated as requested by the CHMP/PRAC. The recalculated incidence rate of completed suicide per 100 subject-years for tildrakizumab is 0.05 and for SIB 0.19. An association between psoriasis and SIB has been thoroughly described in several studies for the overall psoriasis population. No causal association between the treatment with tildrakizumab and the completed suicides has been established. The reported cases of completed suicide are considered not related to the treatment with tildrakizumab although this can never be excluded completely. Additionally the Applicant accepted the proposal to include serious psychiatric events (e.g. completed suicidal, serious depression and SIB) as an outcome of interest in the proposed registry study. For these reasons the implementation of a warning statement in the SmPC is considered not necessary.

The rate of SAEs per 100 patient-years in the Phase 2b and Phase 3 Base Period Safety Pool was similar for the tildrakizumab 200 mg group at 7.21 and the tildrakizumab 100 mg group at 5.81 compared with the placebo group at 6.40, but was higher for the etanercept group at 13.04. Overall the SAE rate was low across treatment groups, with the exception of the Neoplasms SOC. Within this SOC, the highest incidence rate per 100 patient-years was noted for the etanercept group (3.26).

The rate of drug-related SAEs per 100 patient-years was low for the tildrakizumab 200 mg group (0.97), the tildrakizumab 100 mg group (0.30) and the placebo group (0.91), compared with the etanercept group (3.26). The highest drug-related SAE rate across groups was noted for the Infections and infestations SOC.

The rate of AEs leading to discontinuation per 100 patient-years was similar across the treatment groups with the exception for etanercept. The rate for the tildrakizumab 200 mg was 2.15, for the tildrakizumab 100 mg 2.20 and for placebo 2.28. For the etanercept group the rate of AE´s leading to discontinuation was 5.87, which is more than double compared to the tildrakizumab 200 mg treatment group.

Seven (7) deaths occurred in the clinical development program of tildrakizumab. None of the 7 deaths in subjects receiving tildrakizumab is considered to be related to study medication. All patients had related risk-factors in their medical history.

For the subgroup analyses, there were no trends observed in the analysis of gender, BMI, weight, baseline disease characteristics, duration of disease and previous psoriasis treatments. Parameters of one or more adverse events, drug-related adverse events, SAEs, SARs, deaths, discontinuations due to AEs/ARs/SARs/SAEs were compared. There were no meaningful differences seen in the safety profile observed in elderly as compared to younger patients or patients weighing over 90 kg as compared to lighter patients. However the information in elderly is considered limited to draw definite conclusions.

Additionally, pregnancy outcomes will be monitored post authorisation in order to characterise the safety profile during pregnancy.

Hypersensitivity, immunogenicity, SIB, IBD, Infections, MACE and malignancies are included as potential risks in the RMP which is endorsed as long term data beyond week 64 are limited. Long Term Extension Studies are ongoing and will evaluate the long term safety and tolerability of tildrakizumab. (see later)

Overall, the safety profile remains to be further characterised in the post authorisation setting. Therefore, the following studies listed in the RMP have been agreed:

- Long-term safety extension period (up to 4 years) study from study P010 currently ongoing.
- Long-term safety extension period (up to 4 years) study from study P011 currently ongoing.
- Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registry –Planned
- Pregnancy safety related study – planned in US and EU. In the EU the monitoring of pregnancy will be through the above PASS or within a dedicated study.

2.6.2. Conclusions on clinical safety

The overall safety profile of tildrakizumab is in line with other biologicals for the treatment of psoriasis, with the most common adverse events and serious events falling under the infections and infestations SOC.

Data from the Phase 2b/3 Trials Placebo-controlled Safety Pool show that the incidence rate for AEs was comparable between the treatment groups. The most frequently reported SOC was Infections and infestations. The most frequently reported specific AEs were nasopharyngitis and headache.

The rate of Drug-related SAEs was low in the tildrakizumab groups. Hypersensitivity, SIB, IBD, Infections, MACE and malignancies are included as potential risks in the RMP which is endorsed as long term data beyond week 64 are limited. Long Term Extension Studies are ongoing and will evaluate the long term safety and tolerability of tildrakizumab.

There were no meaningful differences seen in the safety profile observed in elderly as compared to younger patients or patients weighing over 90 kg as compared to lighter patients.

2.7. Risk Management Plan

Safety concerns

Important identified risks	**None**
Important potential risks	Hypersensitivity Serious infections Malignancies Major adverse cardiac events Suicidal ideation behaviour (SIB) Inflammatory Bowel Disease (IBD)
Missing information	Safety in pregnant and lactating women Long term safety Use after recent vaccination with live bacterial or live viral vaccines Use in immunosuppressed patients Use in patients with severe hepatic impairment Use in patients with severe renal impairment

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				

Long-term safety extension period (up to 4 years) study from study P010 On-going	To assess the long term safety profile and tolerability of tildrakizumab for up to 4 years. The study will also monitor the tier 1 adverse events which include MACEs, serious infections, malignancies, hypersensitivity reactions and injection site reactions.	Long term safety profile of tildrakizumab	Annual update	Progress report in 2018
			Final report	July 2019
Long-term safety extension period (up to 4 years) study from study P011 On-going	To assess the long term safety profile and tolerability of tildrakizumab for up to 4 years. The study will also monitor the tier 1 adverse events which include MACEs, serious infections, malignancies, hypersensitivity reactions and injection site reactions.	Long term safety profile of tildrakizumab	Annual update	Progress report in 2018
			Final report	July 2019
Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registry Planned	To collect long-term safety data in particular relating to event of special interest (important potential risks and pregnancy related outcomes) for tildrakizumab. To further characterize the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care.	Malignancies MACEs Serious infections SIB Hypersensitivity IBD Safety in pregnant and lactating women	Submission protocol for evaluation	Q4 2018 (3 months after EC decision)
			Annual update	Annual progress report
			Final report	Q4 2030
Pregnancy safety related study 3357-2 (US) Planned	To assess the incidence of major congenital malformations, spontaneous abortions, stillbirths, elective terminations and small for gestational age and other adverse pregnancy outcomes in pregnant women exposed to tildrakizumab	Congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, neonatal deaths and infant infections	Annual update	Within PSUR
			Final report	Jan 2030

Pregnancy safety related study 3357-3 (US) Planned	To evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections	Congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections	Annual update	Within PSUR
			Final report	Jan 2027
Pregnancy safety related study (EU) To be confirmed (Conditional to the non-feasibility of study pregnancy outcomes in the Tildrakizumab Post-Authorisation Safety Study (PASS) in European Psoriasis Registries)	To characterise safety profile of Tildrakizumab when used during pregnancy.	Major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. Additionally, infant outcomes and effects on postnatal growth and development, through the first year of life	To be defined	To be defined*
Tildrakizumab Post authorization observational study (US) 3357-4 Planned	To further characterize the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care. To collect long-term safety data in particular relating to important potential risks for tildrakizumab.	Malignancies Serious Infections MACEs	Annual update	Within PSUR
			Final Report	Feb 2034

*to be implemented in the RMP update

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity	**Routine risk minimisation** • SmPC Sec. 4.3 • PL Sec. 2 • Prescription only medicine	**Additional PV** • Review of safety data from long term (4 years) extension studies • Monitoring of Hypersensitivity in PASS in European Psoriasis Registries
Serious infections	**Routine risk minimisation** • SmPC Sec. 4.3 and Sec. 4.4 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form **Additional PV** • Review of safety data from long term (4 years) extension studies • Monitoring of serious infections in PASS in European Psoriasis Registries • Monitoring of serious infections in US observational Study 3357-4
Malignancies	**Routine risk minimisation** • SmPC Sec. 5.3 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for malignancies. **Additional PV** • Review of safety data from long term (4 years) extension studies. • Monitoring of malignancies in PASS in European Psoriasis Registries • Monitoring of Malignancies in US observational Study 3357-4
Major adverse cardiovascular events (MACE)	**Routine risk minimisation** • None proposed in product information as no increased risk of MACE was observed in clinical development. • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for MACE. **Additional PV** • Review of safety data from long term (4 years) extension studies. • Monitoring of MACEs in PASS in European Psoriasis Registries • Monitoring of MACE in US observational Study 3357-4
Suicidal ideation behavior (SIB)	**Routine risk minimisation** • None proposed in product information as no increased risk of SIB was observed in clinical development. • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for SIB. **Additional PV** • Review of safety data from long term (4 years) extension studies. • Monitoring of SIB in PASS in European Psoriasis Registries
Safety in pregnant and lactating women	**Routine risk minimisation** • SmPC Sec. 4.6 and Sec. 5.3 • PL Sec. 2	**Routine PV** • Specific pregnancy follow-up form **Additional PV**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Prescription only medicine	• Monitoring in PASS in European psoriasis registries • Pregnancy safety related studies 3357-2 and 3357-3 (US) • Pregnancy safety related study (EU)*
Inflammatory Bowel Disease (IBD)	**Routine risk minimisation** • None proposed in product information as no increased risk of IBD was observed in clinical development. • Prescription only medicine	**Routine PV** • None specific **Additional PV** • Review of safety data from long term (4 years) extension studies. • Monitoring of IBD in PASS in European Psoriasis Registries
Long term safety profile	**Routine risk minimisation** • None proposed in product information as no increased risk with long term use was observed in clinical development. • Prescription only medicine	**Additional PV** • Review of safety data from long term (4 years) extension studies • PASS in European Psoriasis Registries • US observational Study 3357-4
Use after recent vaccination with live bacterial or live viral vaccines	**Routine risk minimisation** • SmPC Sec. 4.4 and 4.5 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for "serious infection" includes questions related with vaccination status
Use in immunosuppressed patients	**Routine risk minimisation** • SmPC Sec. 4.5 • PL Sec. 2 • Prescription only medicine	**Routine PV** • Specific ADR follow-up form for "serious infection" includes questions related with immune system status of the patient and questions related with prior and concomitant immunosuppressant medications
Use in patients with severe hepatic impairment	**Routine risk minimisation** • SmPC Sec. 4.2 and Sec 5.2 • Prescription only medicine	**Routine PV** • Periodic review of safety reports with medical history of hepatic impairment
Use in patients with severe renal impairment	**Routine risk minimisation** • SmPC Sec. 4.2 and Sec 5.2 • Prescription only medicine	**Routine PV** • Periodic review of safety reports with medical history of renal impairment

** Conditional to the non-feasibility of study pregnancy outcomes in the Tildrakizumab Post-Authorisation Safety Study (PASS) in European Registries.*

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.03.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that tildrakizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers tildrakizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ilumetri (tildrakizumab) is included in the additional monitoring list as

it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

It is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a chronic, immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological quality of life. Psoriasis is one

of the most common human skin diseases affecting 2 to 3% of the general population. The prevalence of psoriasis varies in the EU from 0.6% to 8.5%. Psoriasis is a chronic, painful immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological quality of life. The uncontrolled inflammation of psoriasis may contribute to commonly associated comorbidities, including cardiovascular (CV) disease (including hypertension and increased risk for myocardial infarction, stroke, and CV death), obesity, type 2 diabetes, arthritis, and chronic renal disease. Psoriasis is also associated with serious psychiatric comorbidities, including depression, anxiety, and suicidality, as well as substance abuse.

3.1.2. Available therapies and unmet medical need

Current therapeutic options for moderate to severe plaque psoriasis include phototherapy, topical agents (e.g., corticosteroids), conventional systemic therapy (e.g., cyclosporine, methotrexate, and oral retinoids), and biologic therapy including TNF-α antagonists (adalimumab, etanercept, infliximab), anti-IL12/IL23, IL23(guselkumab) (and IL-17 inhibitors (ustekinumab, secukinumab, ixekizumab).

3.1.3. Main clinical studies

The clinical development program tildrakizumab consisted of 2 pivotal studies, P010 (reSURFACE1) and P011 (reSURFACE2).

Study P010 was a 64-week, Phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of subcutaneous (SC) administration of tildrakizumab 200 and 100 mg doses. The study consisted of a 4-week screening period, a 12-week Part 1 period (Week 0 to Week 12), a 16-week Part 2 period (Week 12 to Week 28), a 36-week Part 3 period (Week 28 to Week 64), and a 20-week follow-up period. Seven hundred seventy two (772) patients were enrolled of which 638 completed the study.

Study P011 was a Phase 3, randomized, double-blind, active-comparator (etanercept) and placebo-controlled, parallel-group trial to evaluate the efficacy and safety of subcutaneous (SC) administration of tildrakizumab 200 and 100 mg doses. The study consisted of a 4-week screening period, a 12-week Part 1 period (Week 0 to Week 12), a 16-week Part 2 period (Week 12 to Week 28) and a 24-week Part 3 period (Week 28 to Week 52). 756 of initially 1090 patients completed the trial.

Male and female patients 18 years of age or older with a diagnosis of moderate-to-severe chronic plaque psoriasis (defined by ≥10% body surface area [BSA] involvement, “moderate” or greater score on the PGA scale, and PASI score ≥ 12 at baseline were eligible to participate in these trials. The eligibility criteria were adequate for the inclusion of patients with moderate to severe plaque psoriasis.

3.2. Favourable effects

Tildrakizumab is a targeted humanised anti-IL-23p19 mAb. IL-23 is a pro-inflammatory cytokine that has been implicated in the pathogenesis of a number of chronic inflammatory diseases including psoriasis. IL-23 affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease.

Dose response was demonstrated in study P05495. This led to the selection of the tildrakizumab 100 mg and 200 mg for the pivotal studies P010 and P011. The co-primary endpoints of the 2 pivotal studies P010 and P011 were the proportion of patients with PASI 75 response and a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline, at Week 12.

In both pivotal studies both tildrakizumab doses showed a statistically significant higher efficacy to placebo (P010 and P011) and to etanercept (P011) with respect to PASI 75 and PGA responders. The applicant has opted for the 200 mg over 100 mg dose. The efficacy data show that the response to the 200 mg dosing regimen was slightly higher as compared to the 100 mg dosing regimen over time. However, the results of the primary endpoints show that both tildrakizumab doses have similar results in the first 12 weeks of treatment. Small differences arise in both pivotal studies in the late stage of the maintenance period.

For P010 the proportion of patients achieving a PASI 75 response at Week 12 was significantly higher with 63.8% (95%-CI: 58.1 – 69.1%) for the tildrakizumab 100 mg and 62.3% (95%-CI: 56.7 – 67.8%) tildrakizumab 200 mg groups compared with 5.8% (95%-CI: 2.7 – 10.8%) for the placebo group ($p<0.001$ each). Regarding the second co-primary endpoint the proportions of patients with a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12 were significantly greater with 57.9% (95%-CI: 52.2 – 63.5%) in the tildrakizumab 100 mg and 59.1% (95%-CI: 53.4 – 64.6%) in the tildrakizumab 200 mg groups compared with the placebo (7.1%)(95%-CI: 3.6 – 12.4%) group ($p<0.001$ each).

For P011 the proportion of patients achieving a PASI 75 response at Week 12 was significantly greater in the tildrakizumab 100 mg with 61.2% (95%-CI: 55.5–66.7%) and tildrakizumab 200 mg with 65.6% (95%-CI: 60.1-70.9%) groups compared with 5.8% (95%-CI: 2.7-10.7%) in the placebo and 48.2% (95%-CI: 42.6-53.9%) in the etanercept (group ($p<0.001$ each). Regarding the second co-primary endpoint, the proportion of patients with a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12 was significantly greater in the tildrakizumab 100 mg (54.7%)(95%-CI: 44.0-60.4%) and tildrakizumab 200 mg (59.2%)(95%-CI: 53.6-64.7%) groups compared with the placebo (4.5%)(95%-CI: 1.8-9.0%) and etanercept (47.6%)(95%-CI: 42.0-53.3%) group ($p<0.001$ each).

The results of the key secondary endpoints are in line with the primary efficacy analysis, demonstrating superiority of both tildrakizumab arms to placebo.

As secondary endpoints PASI 90 and 100 at different time points were included. These are clinically relevant endpoints. Psoriasis is a chronic disease and the maintenance of response is a very important point especially when it comes to PASI 100. The data for the response rates over time in the Phase 3 trials show that 40% of patients achieve a PASI 100 response at week 36 (P010) and 32 (P011) with a maximum effect at week 48 for the P010 (43.7%) and week 52 for the P011 (46.7%). Symptomatic improvement was also demonstrated with Tildrakizumab treatment as demonstrated on DLQI as well as HAQ scores.

Re-treatment with tildrakizumab after relapse was also effective. Patients who were re-treated after relapse during the withdrawal phase responded to re-initiation of their initial treatment.

Compared to other biologic therapies recently approved (e.g. brodalumab, ixekizumab, secukinumab) the onset of efficacy is slower. However, the efficacy over time is high and the maintenance dosing interval of every 12 weeks is seen favourable as this reduces the burden on the patient.

Both doses were comparable in term of efficacy, therefore the dose regimen of 100mg at weeks 0, 4 and every 12 weeks thereafter was considered more appropriate. However in patients with higher body weight (>90kgs) and in patients with higher disease burden, the dose of 200mg may achieve higher efficacy.

3.3. Uncertainties and limitations about favourable effects

High numbers of protocol deviations have been reported for both studies. The high incidence of protocol deviations triggered the GCP inspections of studies P010 and P011 (GCP/2017/017 and GCP/2017/034). The applicant provided additional sensitivity analyses excluding those entries in order to quantify the relevance of these entries on the results of each study. There were 2 approaches, in which affected entries have been considered as “Non-responder” or all patients with any entry affected have been excluded from the analyses. The results of these analyses showed only small differences regarding the results of the co-primary endpoints (PASI75 and PGA response). Therefore the impact of the protocol deviations is considered negligible for the conclusions on favourable effects.

17.5% of psoriatic patients had received prior biologic therapy and 8.3% had received at least one prior anti-TNFα agent, it is unknown how efficacious tildrakizumab would be in patients with more resistant disease and whom had failed a number of previous prior biological therapies.

Patients were not allowed concomitant moderate to high potency topical steroids or systemic steroids which may be useful in practice, it is unclear whether any additional benefit would be demonstrated or indeed safe to use tildrakizumab in combination with these medicinal products.

The effects of Tildrakizumab on regional psoriasis such as scalp, hand and foot as well as nail psoriasis were not reported on in the trials. Although efficacy was demonstrated in a subpopulation on psoriatic arthritis the numbers are too low to draw any conclusion. It is acknowledged that psoriatric arthritis can affect 15-20% of the population and in some cases can precede the skin changes.

The majority of patients were white and middle aged, while differences in efficacy in different races or ages are not anticipated experience of use in other races is limited. There is also limited information in elderly patients.

The phase 3 studies had different designs for duration of maintenance effect. Pooled data on subgroups was not conducted for maintenance effect the numbers of patients in the subgroup for the individual trials is too low to draw any robust conclusions.

3.4. Unfavourable effects

The overall safety profile of tildrakizumab is 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 etanercept and the adverse events were mainly mild in severity. Tildrakizumab was generally well tolerated in the Phase 1 and 2b PK trials following administration of multiple IV (up to 10 mg/kg) and SC (up to 400 mg) doses. In the Phase 2b/3 efficacy and safety trials involved comparison of both doses 100mg and 200mg tildrakizumab, no dose-related trends were seen in terms of AEs, SAEs, drug-related AEs, discontinuation due to AEs, or Tier 1 AEs in tildrakizumab 100mg and 200 mg doses. The most common adverse events and serious events were falling under the infections and infestations SOC. No differences between the 100 mg and 200 mg doses were observed that would clearly point towards favouring one dose regime, neither in incidence of adverse events nor in type of adverse events.

Almost half of the patients experienced at least one adverse event during the placebo controlled safety pool and this was comparable among treatment arms. One or more AEs was reported in 339 subjects (47.9%) receiving tildrakizumab 200 mg, 340 subjects (48.2%) receiving tildrakizumab 100 mg, 191 subjects (53.8%) receiving placebo, and 169 subjects (54.0%) receiving etanercept. This was also consistent with AE incidence in the base period safety pool and the extension safety pools.

Due to the IL-23 pathway blocking mechanism of action and available experience from similar compounds severe infection, malignancies, NMSC, melanoma skin cancer, Suicidal ideation behaviour, confirmed extended MACE, ISRs, and drug-related hypersensitivity reactions were considered adverse events of special interest.

Overall the incidence of infections and infestations was lower for the tildrakizumab groups compared to etanercept. The exposure-adjusted event rates (per 100 subject-years) of AEs in the Infections and Infestations SOC were 52.64 for the tildrakizumab 200 mg and 48.88 for the tildrakizumab 100 mg group and 86.04 for the etanercept group.

Causal relationship between tildrakizumab and MACE could not be established based on the current data. For the base period safety pool, the incidence of patients with MACE events was reported in 4/1081 (0.4%) and 3/1039 (0.3%) patients from the Tildrakizumab, 100 and 200mg groups, respectively and 1/588 (0.2%) in placebo group. There were no events in the Etanercept group. Hypersensitivity is a potential risk related to monoclonal antibodies. This is included in the potential risks of the RMP.

Overall 2 completed suicides were reported (base pool and extension period), the incidence per 100 subject years was 0.05, the incidence of SIB was 0.19 per 100 subject years in the same analysis population. SIB is included as a potential risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

The overall rate of adverse events is low, only data from a larger patient population over a longer time can give a more precise picture. A long term extension study deriving additional 192 weeks of safety data is ongoing at the moment. The predominant adverse events were infections, the prevalence of which was similar in the tildrakizumab /etanercept arm across the safety pools. As the mechanism of action of tildrakizumab may lead to susceptibility of infections, long term follow-up data needed to better clarify the vulnerability to infections of tildrakizumab treated patients. This will be monitored in the long term follow up safety study as well as in the registries as planned in the RMP.

Malignancies are an important safety aspect of immunomodulatory therapies. The nonclinical data on IL-23 blockade show among others role in resistance to tumour induction in mice, while toxicology studies do not raise significant concerns regarding carcinogenicity. The incidence of malignancy (including non-melanoma and melanoma skin cancer) was comparable to placebo and comparator etanercept in general throughout the safety data pools. However, numerically the majority of malignant diseases were observed in tildrakizumab treated patients, this raises concern, and the possible association with tildrakizumab treatment needs to be further investigated.

Almost 50% of the sera tested through 12-16 weeks in the pivotal studies, were inconclusive. However, there seemed to be no effect of ADA status, positive or negative/inconclusive, on the proportion of subjects achieving the primary and key secondary endpoints of PASI and PGA response at Week 12. After adjustment for exposure, the incidence rate of subjects with 1 or more specific adverse events among ADA positive subjects during the base study was comparable between the tildrakizumab 100 mg and tildrakizumab 200 mg groups. No meaningful differences could be identified to the individual parts of the base study.

In the development program of tildrakizumab a total of 6 cases of SIB have been identified, one occurring in a phase I trial, one case was identified during the base period and 4 additional cases in the extension period. In the long term extension period two completed suicides were reported. Both of these cases, causality assessment of the reported event is considered heavily confounded, and neither event is considered related to tildrakizumab by the investigator or the Sponsor. Serious psychiatric

events (e.g. completed suicidal, serious depression and SIB) were included as an outcome of interest in the proposed registry study. An association between psoriasis and SIB has been thoroughly described in several studies for the overall psoriasis population. The reported cases of completed suicide are considered not related to the treatment with tildrakizumab although this can -not be excluded completely. Nevertheless, the risk of SIB remains unknown and will be monitored in the post authorisation setting.

There are no data in pregnancy. Considering the mechanism of action of tildrakizumab, monitoring of pregnancy outcomes at both doses was considered necessary, therefore this will be monitored in the post marketing setting.

3.6. Effects Table

Effects Table for Tildrakizumab

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
PASI 75	Proportion of patients with PASI 75 response at week 12	%	Tildrakizumab 200mg:64.8% 100mg:62.3%	Placebo: 5.6% Etanercept: 48.2%	Phase 2b and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set
PGA 0/1	Proportion of patients with a PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at week 12	%	Tildrakizumab 200mg:60.0% 100mg:57.2%	Placebo: 5.6% Etanercept: 47.6%	Phase 2b and 3: 12-Week Placebo-Controlled Efficacy Pool Full Analysis Set
PASI90	Proportion of patients with PASI 90 response at week 52	%	Tildrakizumab 200mg: 69.9% (P010) 81.9% (P011) 100mg: 63.7% (P010) 78.4% (p011)	Placebo: N/A Etanercept: N/A	Phase 3 Studies 226 patients/ 113 (P010) 309 patients/ 105 (P011)
PASI 100	Proportion of patients with PASI 100 response at week 52	%	Tildrakizumab 200mg: 43.4% (P010) 46.7% (P011) 100mg: 32.7% (P010) 35.3% (P011)	Placebo: N/A Etanercept: N/A	Phase 3 Studies 226 patients/ 113 (P010) 309 patients/ 105 (P011)
Unfavourable Effects					
Nasopharyngitis	Proportion of Patients	%	Tildrakizumab 200mg: 9.3 100mg: 11.1	Placebo: 8.2 Etanercept: 11.5	Phase 2 and 3 Placebo controlled Safety Pool Placebo until W12-16 Etanercept until W28

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	Number of patients with event per 100-subject-years	n	Continuous* exposure 100/200mg tildrakizumab (23.06)	Placebo (25.13) etanercept (41.06)	52W for P05495 64W for P010. Data relating to etanercept-P011 only
Gastro-intestinal disorders	Number of patients with event per 100-subject-years	n	Tildrakizumab 200mg: 13.24 100mg: 15.83	Placebo: 12.79 Etanercept: 24.77	Exposure Adjusted Phase 2 and 3: Base Period Safety Pool All Subjects as Treated
Musculoskeletal and connective tissue disorder	Number of patients with event per 100-subject-years	n	Tildrakizumab 200mg: 18.30 100mg: 18.33	Placebo: 20.56 Etanercept: 28.68	Exposure Adjusted Phase 2 and 3: Base Period Safety Pool All Subjects as Treated
Severe Infections	Number of patients with event per 100-subject-years	n	Continuous* exposure 100/200mg tildrakizumab (1.00)	Placebo (0.91) etanercept (1.96)	52W for P05495 64W for P010. Data relating to etanercept-P011 only

Abbreviations: W=Week
Notes:
*Includes subjects who stayed on one of the 100 mg or 200 mg throughout the whole Base period.

3.7. Benefit-risk assessment and discussion

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population. The prevalence of psoriasis varies in the EU from 0.6% to 8.5%. Psoriasis is a chronic, painful immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological quality of life. The conventional therapies are associated with dose- and treatment-limiting options. The most common reasons for discontinuation of these therapies are lack of efficacy, adverse events (AEs) and treatment inconvenience. However, newer treatment options provide improved outcomes compared with traditional systemic therapies.

Tildrakizumab is a new targeted biological treatment for patients with plaque psoriasis. Tildrakizumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23 mediated intracellular signalling, activation and cytokine production.

It has been demonstrated to work effectively in a heterogeneous population who were recruited into the study and a significant proportion of patients achieved PASI 75 and PGA responses. In the two pivotal Phase 3 Studies both tildrakizumab groups showed a statistically significant higher and clinically meaningful efficacy relative to placebo (P010 and P011) and to etanercept (P011) with respect to PASI 75, 90, 100 and PGA response at different timepoints. Patient reported outcomes e.g. DLQI improved parallel with the therapeutic effect.

The pivotal trials encompassed two doses of tildrakizumab. The doses gave very similar results for pivotal efficacy demonstration as well as for safety. Analyses of PK showed that body weight is an important factor in determining exposure and therefore the CHMP considered that the agreed posology with the more favourable benefit /risk to be the lower dose of 100 mg. Possibility to consider higher dose of 200mg (with two injections) in patients of >90 kg and with a higher disease burden may also be considered acceptable in these patients.

The onset of efficacy is apparently not as fast as other approved biologic therapies. However, after 12 weeks of treatment over 60% of the patients showed PASI 75 in both tildrakizumab groups. The

proportion of patients with a PASI 100 response at week 12 was 13.3% in the tildrakizumab 200 mg group, 13.5% in the tildrakizumab 100 mg group compared to 5.2% in the etanercept group. The highest results for PASI 100 are seen not earlier as week 32 in both pivotal studies. At this time around 40% of patients treated with tildrakizumab achieved PASI 100 response. This rate was maintained till the end of the studies.

Due to the IL-23 pathway blocking mechanism of action and available experience from similar compounds severe infection, malignancies, NMSC, melanoma skin cancer, SIB, confirmed extended MACE, ISRs, and drug-related hypersensitivity reactions were considered adverse events of special interest.

Regarding malignancies the role of the cytokine-blockade might be multiple and so far the diagnosed malignancies in clinical trials were not unequivocally connected to tildrakizumab. Longer experience is needed to get more information about the risk of malignancies. Effects on cardiovascular system remains also to be explored in the long term extension study, so far few cases were reported. For the fatal cardiovascular events in the development program of tildrakizumab pre-existing risk factors were present.

Overall, the rates of adverse events and serious adverse events were comparable between both tildrakizumab groups and placebo, while etanercept showed higher rates of adverse events. Adverse events of special interest such as infections, MACE, and malignancy, would benefit from long term follow-up data needed to better clarify the vulnerability to these risks for tildrakizumab treated patients.

Regarding the available safety data, to date one to two year data are available on tildrakizumab therapy with a long-term extension period ongoing. This period is not long enough to fully characterize the favourable and unfavourable effects observed with tildrakizumab, therefore the applicant will monitor long term data in the clinical setting (category 3 study in the RMP). As the overall frequency of adverse events is low, only data from larger patient population over a longer time will give a more real picture.

3.7.1. Balance of benefits and risks

Statistically significant and clinically relevant efficacy of tildrakizumab has been shown. Total clearing of the psoriatic skin can be achieved which is considered of high relevance to the patient. This is accompanied by a safety profile, which has a low rate of adverse events in clinical trials and with no specific pattern of serious adverse events which seem to be rather sporadic events. Based on the data presented, the beneficial effects are considered to outweigh the unfavourable effects seen in the clinical programme. Long term experience with tildrakizumab is available from the pivotal studies up to week 64, as well as from the ongoing long term extensions (as per cut-off date May 2017, 57.8% of all subjects exposed during Phase 2b and Phase 3 have received treatment for at least 2 years) but this is still considered limited. Long Term Safety Extension Studies are ongoing to evaluate the efficacy and safety of long term use in the clinical setting up to 4 years to further characterise the safety profile post marketing. Additionally registries will be set up as described in the RMP.

3.7.2. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R balance of Ilumetri is positive in adult patients with moderate to severe plaque

psoriasis.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ilumetri is favourable in the following indication: Treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tildrakizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union