14 September 2017
EMA/692068/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tremfya

International non-proprietary name: guselkumab

Procedure No. EMEA/H/C/004271/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Tremfya
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	GUSELKUMAB
International Non-proprietary Name/Common Name:	guselkumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, interleukin inhibitors (not yet assigned)
Therapeutic indication(s):	Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Pharmaceutical form(s):	Solution for injection (injection)
Strength(s):	100 mg
Route(s) of administration:	Subcutaneous use
Packaging:	pre-filled syringe (glass)
Package size(s):	1 pre-filled syringe

Table of contents

List of abbreviations

ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AUC	area under the concentration versus time curve
$AUC_{0\text{-}28week}$	cumulative area under the concentration time curve up to Week 28
BSA	body surface area
C_{ave}	average daily serum guselkumab concentration
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	systemic clearance
CL/F	apparent total systemic clearance of drug after extravascular administration
C_{max}	maximum observed concentration
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DBL	database lock
DELFIA	dissociation-enhanced lanthanide fluorescent immunoassay
DLQI	Dermatology Life Quality Index
ECLIA	electrochemiluminescence immunoassay
EP	erythromdermic psoriasis
FDA	Food and Drug Administration
f-PGA	fingernail Physician's Global Assessment
HADS	Hospital Anxiety and Depression Scale
hf-PGA	Physician's Global Assessment of hands and/or feet
HPRA	Health Products Regulatory Authority
GPP	generalized pustular psoriasis
IBD	inflammatory bowel disease
IGA	Investigator's Global Assessment
IgG1λ	immunoglobulin G1 lambda

IL	interleukin
ISR	injection-site reactions
IV	intravenous
k_a	first-order absorption rate constant
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MSD	Meso Scale Discovery
MTX	methotrexate
n	sample size
NA	North America
NAPSI	Nail Psoriasis Area and Severity Index
NMSC	nonmelanoma skin cancer
PASI	Psoriasis Area and Severity Index
PFS	prefilled syringe
PFS-U	prefilled syringe assembled with a passive needle guard
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PPP	palmoplantar pustulosis
PRO	patient-reported outcome(s)
PsA	psoriatic arthritis
PSSD	Psoriasis Symptom and Sign Diary
PUVA	psoralen plus ultraviolet therapy
q2w	every other week
q4w	every 4 weeks
q8w	every 8 weeks
q12w	every 12 weeks
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous, subcutaneously
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SF-36	Medical Outcomes Study 36-Item Short Form
SIB	suicidal ideation and behavior
SOC	system-organ class
ss-IGA	scalp-specific Investigator's Global Assessment
$T_{1/2}$	terminal half-life
TB	tuberculosis
Th1	T-helper 1
Th17	T-helper 17
T_{max}	time to reach the maximum serum concentration
TNFα	tumor necrosis factor alpha
URTI	upper respiratory tract infection
USA	United States of America
UVB	ultraviolet B
Vz	volume of distribution during the terminal phase
V/F	apparent volume of distribution based on the terminal phase after extravascular administration
WLQ	Work Limitations Questionnaire

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 23 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Tremfya, through the centralised procedure falling within the Article 3(1) and point 1of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that guselkumab was considered to be a new active substance.

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/0073/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance guselkumab 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 did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Agnes Gyurasics Co-Rapporteur: David Lyons

- The application was received by the EMA on 23 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.

  The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 June 2017.
- During the PRAC meeting on 6 July 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 September 2017.
- During the meeting on 11-14 September 2017, 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 Tremfya on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for guselkumab is as follows:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriasis is a chronic, non-communicable, painful, immunologically-mediated, disfiguring and disabling inflammatory skin disease for which there is no cure and with great negative impact on patients' quality of life (QoL).

2.1.2. Epidemiology

Plaque psoriasis affects 2% to 4% of the general population[1,2,3,4,5,6]. Psoriasis is uncommon before the age of 9 years, with a first peak of psoriasis generally occurring after the age of 20 with an increasing trend with age until around 60 years, after which the incidence is lower[5].

Approximately 90% of those affected with psoriasis have plaque psoriasis[7,8,6], with 20% having moderate to severe plaque psoriasis with a body surface area (BSA) involvement of >5%[9].

2.1.3. Aetiology and pathogenesis

The pathogenesis of psoriasis involves environmental factors and immune dysregulation in genetically-predisposed individuals[10, 11]. Substantial evidence indicates that IL-23 plays an important role in innate and adaptive immune responses, and may play a pivotal role in the pathogenesis of psoriasis vulgaris[12,13,14].

[1] Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-271
[2] Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life enhancement. Dermatol Clin. 1996;14(3):485-496.
[3] Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis : Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58:5:826-850
[4] Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361(5):496-509
[5] Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-385
[6] Schön MP, Boehncke W-H. Medical Progress Psoriasis. N Engl J Med. 2005;352(18):1899-1912
[7] Boehncke WH/ Etiology and pathogenesis of psoriasis. Rheum Dis Clin North Am. 2015;41(4):665-675
[8] Lebwohl M. Psoriasis. Lancet. 2003;361(9364):1197-204
[9] Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis : Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58:5:826-850
[10] Eder L, Chandran V, Gladman DD. What have we learned about genetic susceptibility in psoriasis and psoriatic arthritis? Curr Opin Rheumatol. 2015;27(1):91-98.
[11] Lara-Corrales I, Xi N, Pope E. Childhood psoriasis treatment: evidence published over the last 5 years. Rev Recent Clin Trials. 2011;6(1):36-43
[12] Aggarwal S, Ghilardi N, Xie M-H, et al. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of Interleukin-17. J Biol Chem. 2003;278:1910- 1914
[13] 24. Hong K, Chu A, Lúdviksson BR, Berg EL, Ehrhardt RO. IL-12, independently of IFN-gamma, plays a crucial role in the pathogenesis of a murine psoriasis-like skin disorder. J Immunol. 1999;162(12):7480-7491
[14] Yawalkar N, Karlen S, Hunger R, Brand CU, Braathen LR. Expression of interleukin-12 is increased in psoriatic skin. J Invest Dermatol. 1998;111(6):1053-1057

2.1.4. Clinical presentation

Clinically, plaque psoriasis is characterized by symmetrically distributed, well-defined, sharply demarcated, indurated, erythematous plaques that are covered by friable, dry, white-silvery scale. Areas of the body that are frequently involved include the scalp, elbows, knees, buttocks, and genitalia. The extent of skin involved varies among affected individuals, and is a primary determinant of severity. Psoriasis typically follows a chronic relapsing and remitting course around an individual's underlying baseline severity, with flare-ups occurring spontaneously or during times of illness, or psychological stress.

Although psoriasis is rarely life-threatening, the psoriatic lesions are often on visible skin and unsightly. Patients experience shedding of scale and bleeding from their plaques as well as pain and itching. In addition to these common physical signs and symptoms, patients with moderate to severe psoriasis often experience feelings of self-consciousness and embarrassment, and as a result, may suffer depression, social isolation, and unemployment; all factors which contribute to a significant reduction in overall patient quality of life[15]. For all of these reasons, the disease often requires chronic treatment, particularly for patients with moderate to severe disease.

In addition to the physical and psychological impact of disease, psoriasis is associated with specific co-morbidities, including psoriatic arthritis (PsA), obesity, diabetes, cardiovascular disease, metabolic syndrome, and inflammatory bowel disease (IBD)[16]. It is estimated that between 6% and 42% of psoriasis patients develop PsA[17,18,19]. Psoriasis has also been shown to be associated with a significantly increased risk of Crohn's disease (relative risk, 3.86, 95% confidence interval [CI] 2.23 to 6.67), which is especially pronounced among psoriatic patients with concomitant PsA (relative risk, 6.43, 95% CI 2.04 to 20.32)[20]. Psoriasis is also associated with an increased risk of occlusive vascular disease, including myocardial infarction (MI) and stroke[21]. Multiple cardiovascular risk factors are associated with psoriasis (eg, diabetes and obesity) and are more prevalent in severe disease[22], though psoriasis may also be an independent risk factor for MI. Several large epidemiologic studies have further demonstrated an association between the magnitude of cardiovascular risk and severity of psoriasis[23,24].

2.1.5. Management

The traditional paradigms for the treatment of psoriasis recommend a stepwise approach to treatment starting with topical agents, followed by phototherapy, then systemic agents[25].

[15] Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the national psoriasis foundation survey data 2003-2011. PLoS One. 2012;7(12):e52935
[16] Mrowietz U, Elder JT, Barker J. The importance of disease associations and concomitant therapy for the longterm management of psoriasis patients. Arch Dermatol Res. 2006;298(7):309-319
[17] Green L, Meyers O, Gordon W, Briggs B. Arthritis in psoriasis. Ann Rheumatic Diseases. 1981;40:366-369
[18] Shbeeb M, Uramoto K, Gibson L, et al. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol. 2000;27:1247-1250
[19] Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. Am J Clin Dermatol. 2003;4:441- 447
[20] Li W-Q, Han J-L, Chan AT, Qureshi AA. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. Ann Rheum Dis. 2013;72(7):1200- 1205
[21] McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol. 1978;99(5):469-475.
[22] Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55(5):829-835
[23] Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735-1741
[24] Mallbris L, Akre O, Granath F, Yin L, Lindelof B, Ekbom A, Stahle-Backdahl M. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol. 2004;19(3):225-230
[25] Ashcroft DM, Po AL, Griffiths CE. Therapeutic strategies for psoriasis. J Clin Pharmacol Ther. 2000;25(1):1-10

Most commonly, a 2-tiered system is recommended, divided by patients who are candidates for localized therapy and should receive topical agents versus those who are candidates for systemic and/or phototherapy[26]. Patients who are candidates for systemic and/or phototherapy include those who have moderate to severe disease based on the percentage of BSA involvement and/or plaque location with associated quality-of-life issues.

Conventional systemic therapies include MTX, acitretin, and cyclosporine. Although effective, each is associated with significant toxicities, particularly organ damage with long-term administration, and each agent has recommended limitations for long-term administration.

Rotational therapy is employed to minimize these significant side effects[27], though no evidence exists that rotational strategies can lessen the risk of serious adverse events (SAE)[28].

A variety of biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, etanercept), an IL-12/23 antagonist (ustekinumab), and more recently, IL-17A inhibitors (secukinumab and ixekizumab). These agents are generally well-tolerated, and unlike conventional systemic agents, are not associated with cumulative toxicities that limit longer-term safety. However, as immunomodulatory agents they have the potential to increase risk for infection and malignancy. Concerns for anti-IL-17 class agents also include Crohn's disease, neutropenia, and mucosal candida infections.

While conventional and systemic therapeutic modalities are available for the treatment of moderate to severe plaque psoriasis, most do not provide adequate efficacy to a majority of patients when assessed using clinically meaningful endpoints such as an Investigator's Global assessment (IGA) of cleared (0) or minimal (1), and PASI 90 and PASI 100[29]. While the response rates of available treatments, including those for more stringent measures of efficacy[30,31], have increased over time, there is still substantial room for improving the proportion of patients that achieve clear skin. In addition, the currently available treatments have practical limitations due to tolerability, toxicity, safety risks, and/or issues with ease of use or convenience.

About the product

Guselkumab is a human mAb directed against the p19 subunit of IL-23 and thus, specifically targets IL-23. A rapidly growing body of literature suggests that the IL 23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immunemediated diseases, including plaque psoriasis, erythrodermic psoriasis (EP), generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), IBD, ankylosing spondylitis, and PsA. Susceptibility to psoriasis, PsA, and IBD has been shown to be associated with genetic polymorphisms in IL-23/IL-23R components.

The proposed indication for guselkumab in the treatment of plaque psoriasis is as follows:

[26] Pariser DM, Bagel J, Gelfand JM, et al. National Psoriasis Foundation Clinical Consensus on Disease Severity. Arch Dermatol. 2007;143:239-242
[27] Sterry W, Barker J, Boehncke WH, et al. Biological therapies in the systemic management of psoriasis: International Consensus Conference. Br J Dermatol. 2004;151(suppl 69):3-17
[28] CHMP/EWP/2454/02corr. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. Available at: http://www.emea.eu.int/pdfs/human/ewp/245402en.pdf. Accessed 18 Nov 2004
[29] Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator' s Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatol Treatment. 2015;26:1:23-31.
[30] Griffiths CEM, Reich K, Lebwohl M, et al, for the UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two Phase 3 randomised trials. Lancet. 2015;386:541-551
[31] Langley RG, Elewski BE, Lebwohl M, et al, for the ERASURE and FIXTURE Study Groups. Secukinumab in plaque psoriasis- results of two phase 3 trials. N Engl J Med. 2014;371:4:326-338.

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Guselkumab is administered by subcutaneous injection. The recommended dose is 100 mg at Weeks 0 and 4, followed by maintenance dosing every 8 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.

Type of Application and aspects on development

This is an application for centralized procedure according to Art. 3(1) (mandatory scope) of Regulation (EC) 726/2004, Annex (1) (Biotech medicinal product).

The application has been submitted in accordance with Art. 8(3) (full application) of Directive 2001/83/EC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 100 mg of guselkumab as active substance. Other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

Tremfya is administered by subcutaneous injection and is available in a prefilled glass syringe with a fixed needle and a needle shield, assembled in a needle safety device.

2.2.2. Active Substance

General Information

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that neutralizes the biological activities of human cytokine, IL-23. IL-23 is a heterodimeric cytokine, which is comprised of 2 protein subunits.

The mechanism of action of guselkumab is prevention of extracellular IL-23 binding to cell surface IL-23 receptor (IL-23R). The binding of guselkumab to the IL-23p19 subunit blocks the binding of IL-23 to the IL-23 receptor, inhibiting IL-23-specific intracellular signalling and subsequent activation and cytokine production.

The intact molecule contains 2 identical heavy chains (HC) of 447 amino acids (approximately 49 kDa each) and 2 identical light chains (LC) of 217 amino acids (approximate 23 kDa each). The 4 chains are linked together by covalent disulfide bonds and non-covalent protein-protein interactions. The HC and LC amino acid sequences have been provided in the dossier. The disulfide bonds were predicted from the expected pairings for a human IgG1 antibody and confirmed by peptide mapping. N-linked glycans were shown to be bi-antennary structures typical for an IgG1 antibody expressed in CHO cells as determined by oligosaccharide mapping with mass spectrometry analysis.

Manufacture, characterisation and process controls

Description of the manufacturing process and process controls

The manufacture of Tremfya active substance represents a standard monoclonal antibody manufacturing. Tremfya active substance is manufactured in a process consisting of fed batch cell culture followed by purification and formulation, which takes place at Biogen (BIIB), Research Triangle Park, NC, USA, and Janssen Biologics (Ireland), Cork, Ireland (JBIL). The listed manufacturers and contract laboratories have been qualified to perform manufacturing, storage and control of guselkumab active substance in compliance with GMP.

During the first stages guselkumab is produced by fed batch fermentation in a production bioreactor, followed by Protein A affinity chromatography, viral inactivation and neutralization. The next stages contain various chromatography steps, virus removal filtration and finally the preparation of the active substance.

Batch numbering is clearly defined. The manufacturing process is clearly presented and in sufficient detail. Critical and non-critical process parameters are listed for all stages, together with respective target values and Proven Acceptable Ranges (PARs). The basis for establishing PARs is process development and/or historical data.

The container and closure used for storage and shipping meet the requirements of: USP <661> Physicochemical Tests - Plastics; USP <87> In-vitro Biological Reactivity Tests; USP <88> In-vivo Class VI Plastics; Ph. Eur. 2.6.9, Abnormal Toxicity; Regulation (EU) No 10/2011, Plastic Materials Intended to come into Contact with Food. The silicone liner meets the requirements of Ph. Eur. 3.1.9, Silicone Elastomer for Closures and Tubing. The container and closure system also complies with the European requirements on leachables and extractables outlined in CPMP/QWP/4359/03.

The containers and closures are supplied pre-sterilized and gamma irradiated. Studies demonstrated that the container closure system maintains integrity during freezing, storage, shipping, and thawing,

Controlled extraction study was performed on representative pre-sterilized containers. The estimated maximum daily exposure of the most abundant extractable is less than the safety threshold described in ICH M7.

Control of materials

The genes encoding for guselkumab were used to transfect CHO cells. The resulting CHO cell line, designated as C1707B, was used to produce material for all clinical trials and will be used to produce commercial product. Culture media formulations are described and all necessary details are provided.

A banking system is used to ensure supply of the production cell line. Tests used for the Master Cell Bank (MCB) are acceptable and in line with the requirements of ICH Q5D and Q5A. Analytical methods are sufficiently described. Isoenzyme analysis was also part of the test panel. According to the certificate of analysis all parameters were compliant.

The test panel for the Working Cell Bank (WCB) is acceptable and is in line with ICH Q5A. Certificates of analysis demonstrate that the cell banks are compliant with the requirements. Preparation and storage of the cell banks are presented in detail, including a protocol for preparation of future WCBs.

Animal- and human-derived components, used during the generation of the development cell banks, have been described and are deemed to be acceptable.

Details of compendial materials have been provided as well as in-house specifications for non-compendial materials including buffer components and chromatography resins.

Control of critical steps and intermediates

In-process controls (IPCs), i.e. tests and the associated acceptance criteria, or predefined instructions have been provided. These were established based on the control of active substance critical quality attributes (CQAs) at critical steps and intermediates to ensure product quality and consistency during the active substance manufacturing process. The applicant also uses process-monitoring tests (PMTs) to ensure process consistency and to add further control on the manufacturing process. PMTs have either action limits or predefined instructions. The strategy applied by the company is considered acceptable.

Description of the AVA (in vitro Adventitious Virus Assay) has also been provided.

Process validation

The applicant provided a detailed and well organized description of the process validation and evaluation data, which is in line with the *Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014).*

Process validation has been performed. Validation of the reprocessing steps, process hold times, resin lifetime and control of impurities has been presented. Shipping was qualified using minimum and maximum shipping conditions. With regard to hold times, these were established based on extensive stability studies.

Chromatography resin lifetimes were established using qualified scale down models and the proposed resin lifetimes are acceptable.

The proposed hold times have been supported by product quality and microbial control data generated using scale down models and using commercial scale material. Microbiological hold time validation was performed, demonstrating acceptable microbial control during maximum hold times for the active substance manufacturing process.

Process validation and evaluation studies confirmed that the applicant is capable of producing the active substance with consistent quality, and this is demonstrated by characterization and batch analysis results of primary structure, carbohydrate structure, disulphide bonds, mass heterogeneity, charge heterogeneity, size heterogeneity and purity, higher order protein structure, and potency.

Shipping of the active substance has been successfully validated.

Process development

A detailed description has been provided on the manufacturing process development, including the history of process development at each of the manufacturing stages, comparability studies, an impurity risk evaluation, process control strategy development, analytical history and the description of the quality management system.

Details of the changes during development as well as a thorough comparability study according to ICH Q5E were presented in the dossier.

The history of the analytical development has also been provided.

A comprehensive description has been provided about the integrated control strategy applied, that was based on identification of critical quality attributes (CQAs) and includes an integrated control of process parameters, material attributes, IPCs, release and stability tests, process validation and procedural control. Prior product knowledge and platform manufacturing experience have also been utilized for the development of the control strategy.

The CQAs are considered relevant for monoclonal antibodies and are controlled through critical process parameters, IPCs or at the release specification level. Elements of Quality by Design were used (Design of Experiments (DoE) for several process steps) but no regulatory flexibility has been claimed. For establishing CPP PARs, some of the experiments were performed in a multivariate fashion wherein more than one PAR was investigated at the same time.

Process related impurities were critically assessed to determine their impact on product safety.

Characterisation

The active substance has been extensively characterised with respect of structure and biological function.

The amino acid sequence as expected on the basis of the cDNA sequence was confirmed by adequate techniques. The known disulphide bond structure of the G1 subclass of immunoglobulins has likewise been confirmed. The intact protein masses corresponded to the major glycoforms. The site of glycosylation on the heavy chain has been identified and the results of an adequate analysis of the carbohydrate side chain variants have been presented. The targeted functional effect of guselkumab binding was demonstrated by a cell based assay where the inhibition of initial IL-23R signaling was quantified. The potency assay reflects the proposed mechanism of action. FcγRI and FcRn binding have also been demonstrated. The structural and biological characterization of guselkumab is deemed satisfactory.

The characterization of structure/function relationships was used to evaluate the criticality of post-translational modifications (PTMs) for guselkumab. This approach helped identify critical points of manufacturing process validation and analytical controls of the active substance and the finished product. The approach used for controlling the product related variants and impurities is deemed adequate.

The removal of process related impurities is addressed at the process validation level.

Specification

The active substance specification includes tests for colour, pH, identity, charge heterogeneity, purity, quantity and microbiological contamination.

The Applicant outlined the strategy followed in establishing the specifications and acceptance criteria and discussed how CQAs were controlled either at the active substance specification or at the in-process control level. Active substance specifications including those of identity, colour of solution, bioburden and endotoxin content were based on regulatory requirements. Other active substance specifications were derived from statistical analysis of release and stability results of the active substance batches used to manufacture Phase 3 clinical finished product. The approach followed is deemed reasonable.

Analytical methods

The active substance specification allows adequate control of identity, purity and potency. For assessing the biological activity a cell based assay was developed which measures guselkumab-mediated inhibition of IL-23 dependent receptor signalling. The assay measures guselkumab bioactivity at the initiation of the IL-23 signaling cascade. The analytical tests and their validations have been described except for bioburden which is a compendial test.

Batch analysis

Data presented include batches of Phase 3 process material, process validation batches and post-process validation batches. The acceptance criteria provided are the Phase 3 and process validation specifications that were in place at the time of release.

Reference materials

The first reference material (RM), called Research Reference Material was prepared from a GMP active substance batch and used for testing Phase 1/2 and Phase 3 clinical batches until the first commercial process primary reference material (PRM) and working reference material (WRM) became available. The RRM was qualified using the release tests and additional characterisation methods, which were in place at that stage of development.

PRM and WRM were qualified using routine release tests along with additional characterization methods.

The procedure for the generation and qualification of the future reference material has been adequately described.

Stability

Analytical methods used are the same as those used for active substance and finished product testing. Samples subject to the stability studies were stored in containers representative of the intended commercial storage containers.

Stability has been demonstrated based on real time data from Phase 3 Process batches.

The stability data submitted generally support the proposed shelf life at the recommended storage condition. The stability indicating parameters are acceptable and the stability monitoring program conforms to ICH Q5C.

Finished Medicinal Product

Description of the product and Pharmaceutical Development

Tremfya finished product is supplied in a single use prefilled syringe (PFS) containing 100 mg active substance/syringe. Composition of the finished product is the same as that of active substance, i.e. 100 mg active substance (guselkumab), sucrose, histidine buffer, polysorbate 80.

The container closure system for the finished product is a sterile, ready to fill 1-ml syringe barrel (clear type I borosilicate glass) with a stainless steel needle. Primary packaging also includes a latex-free rigid needle shield and a rubber plunger stopper which complies with Ph. Eur. 3.2.9 *Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders*. The syringe barrel and plunger stopper are siliconized; data is presented in the pharmaceutical development

section to support acceptably low levels of silicone leaching into the finished product and a specification is applied by the supplier to limit levels of silicone in the syringe barrel.

The syringes are assembled into a passive needle guard. The needle guard is intended to protect against needle-stick injury and automatically extends beyond the PFS needle following complete injection of the PFS contents.

The excipients are compendial and have been sufficiently described. No excipients of human or animal origin and no novel excipients are used in the manufacture of the finished product.

CQAs were discussed as part of the manufacturing process development; the process and its control were developed based on the quality target profile for the product and platform manufacturing experience with the pre-filled syringe at the commercial manufacturing facility. An integrated control strategy which takes into account parametric controls (including CPPs and appropriate PARs), material controls, in-process controls, release/stability testing, characterisation and process validation has been presented. Taken together these control elements ensure that the finished product will meet the defined CQAs. A description of the control points for the CQAs relevant to each manufacturing process step has been provided.

The suitability of the container closure system has been adequately justified with reference to potential impurities and container closure integrity. The risk of glass delamination is determined to be low on the basis of the manufacturing process for the syringes, the finished product formulation/recommended storage conditions and the absence of terminal sterilisation.

Manufacture of the product and process controls

The finished product is manufactured at Cilag AG, Schaffhausen, Switzerland and released at Janssen Biologics B.V., Leiden, The Netherlands.

The finished product manufacturing process includes thawing and pooling of active substance, pre-filtration followed by sterile filtration, and finally aseptic filling into syringes. Relevant IPCs have been identified and acceptance criteria have been determined.

CPPs were determined for the relevant steps of the manufacturing process, i.e. sterile filtration and aseptic filling/stoppering. Proven Acceptable Range (PAR) of the CQAs have been determined.

The manufacturing process and process controls for the assembly of the passive needle guard have been described.

IPC tests are performed by in-line sensors and detectors. Filter integrity and bioburden testing of filters as well as aseptic fill-weight and stopper position are controlled as critical steps.

Manufacturing process validation was performed and all results showed compliance with pre-determined acceptance criteria and commercial release specifications.

The maximum hold time from active substance thawing up to filling and stoppering was validated.

Several phase 3 and validation batches were tested to ensure that IPCs and their respective acceptance criteria are suitable to ensure that the finished product conforms to its release specifications.

Needles were tested and results show no adverse effect on the quality of the finished product. Further leachables and extractables from the container closure system have been evaluated and no issues identified.

The finished product shipping includes various shipping configurations that were validated for different periods of time and temperature ranges.

Product specification

The finished product spectifications include tests for colour, pH, osmolality, turbidity, particulate matter, polysorbate 80 concentration, expelled volume, identity, charge heterogeneity, purity, quantity, potency, pyrogens, microbiological contamination, appearance of primary container and glidability. 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).

Product related impurities were discussed in the active substance section of the dossier but confirmation has been provided that the purity methods for finished product release are adequate for their control.

Analytical methods

The analytical tests and their validations have been described.

Batch analysis

Batch analysis data of the 100 mg presentation were provided.

Reference materials

The reference standards are described in the active substance section.

Stability of the product

The proposed shelf-life time is 24 months from the manufacturing date of the PFS and the recommended storage temperature is 2-8 °C. A comprehensive stability program was conducted for the finished product to assess the effects of storage on the quality parameters.

Overall the proposed shelf life of 24 months at 2-8 °C when the finished product is protected from light is sufficiently justified.

To test finished product stability in a potential event of temperature excursions that may be encountered during transportation, storage, and handling, a thermal cycle stability test was performed.

Photostability studies have demonstrated that the finished product is not stable when exposed to light. The SmPC consequently includes a statement that the product should be stored in the outer carton in order to protect it from light.

Functionality of the passive needle guard over the proposed shelf life has been demonstrated.

Adventitious agents

Animal-derived materials were used only during the generation of the development cell banks, and sufficient information on these materials has been provided. No animal or human derived materials are used during the manufacturing process.

Cell banks were tested for adventitious viruses, the only positive result was for RVLPs.

Reduced scale models used in the viral-clearance studies were qualified for representativeness of the manufacturing process. The virus selection is considered acceptable and process samples were evaluated for suitability in the virus detection system. The purification process provides an acceptable viral clearance to assure viral safety of the finished product.

Medical device

The passive needle guard is an accessory to a glass PFS conforming to ISO standards. It has been demonstrated that the materials used for the passive needle guard components are not adversely affected by aging or storage conditions.

2.2.3. Discussion and conclusions on the 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 satisfactory 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 the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical testing strategy to support development of guselkumab for treatment of psoriasis was designed and conducted in accordance with the International Conference on Harmonisation (ICH) guidance ICH S6 (prior to June 2011) and thereafter ICH S6 (R1) for the preclinical safety evaluation of biotechnology-derived pharmaceuticals and other applicable guidance's.

Pivotal studies in the toxicology program were conducted in accordance with international GLP regulations. In all GLP studies, deviations from the protocol and GLPs were documented and their impact on the interpretation of the study was assessed. Exceptions to GLP were described.

Non-pivotal studies were conducted in accordance with protocols (and amendments where applicable) and Standard Operating Procedures consistent with the principles of GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Guselkumab specifically binds to the p19 subunit of IL-23 with high affinity; it does not bind to the shared p40 subunit of IL-12 and IL-23. Guselkumab binds only to soluble IL-23 and not to the prebound molecule. The neutralization of IL-23 occurs before the binding of IL-23 to its receptor IL-23R. Consequently, Fc portion of guselkumab is not able to activate the complement dependent cytotoxicity.

Guselkumab clearly inhibited IL-23 induced phosphorylation of STAT3 and consequently IL-10 production of NK cells. That shows that blocking IL-23 before it's binding to IL-23R has significant downstream consequences in the immune response. This functional effect was further substantiated by the inhibition of IL-17A, IL-17F and IL-22 production by mouse splenocytes and IL-17 production by

peripheral blood mononuclear cells (PBMC). The in vitro activity of guselkumab to neutralize IL-23 is comparable with that of ustekinumab.

In the cross-species studies it has been shown that guselkumab can fully inhibit IL-17A production by mouse splenocytes induced by native human, guinea pig, primate and cynomolgus monkey IL-23. Guselkumab can only partially inhibit canine IL-23 induced IL-17A production and has no effect at all on mouse and rat IL-23 induced IL-17A production. Recombinant human, cynomolgus, rat and mouse IL-23 showed similar sensitivity to guselkumab to their native counterparts, respectively. It was also demonstrated that guselkumab can inhibit recombinant cynomolgus IL-23 induced IL-17A and IL-17F production by cynomolgus T cells. These latter data suggest that guselkumab might act similarly on the IL-17A production by human T cells as cynomolgus monkeys are genetically much closer to humans than mice.

Human IL-23 seemed to increase serum levels of several cytokines in mice. Intraperitoneal (i.p.) administration of both recombinant mouse (rm) IL-23 and rhIL-23 to C57BL/6 mice was found to result in dose dependent increases in serum levels of IL- 1α, G-CSF, IP-10, TNFα, GM-CSF and MCP-1. Guselkumab administration was shown to attenuate rhIL-23 induced increases in serum levels of cytokines IL- 1α and G-CSF without any significant change in TNFα, IP-10 or GM-CSF levels.

Secondary pharmacodynamic studies

No in vivo secondary pharmacodynamic studies were performed. Due to the high specificity of guselkumab demonstrated in the in vitro studies it was deemed unnecessary to search for secondary targets in mice or rats.

Secondary pharmacological in vitro studies investigated the tissue cross reactivity of guselkumab. A non GLP study demonstrated that the biotinylation of guselkumab did not appear to affect tissue staining patterns, and hence biotinylated guselkumab was used for further studies. Tissue cross reactivity studies revealed that biotinylated guselkumab exhibits similar cross tissue reactivity in both human and cynomolgus monkey. There was extensive staining of both cardiac and skeletal myocytes in both species, the entire cytoplasm of cardiac myocytes was stained while the staining was primarily localised in the peripheral cytoplasm of skeletal myocytes.

Guselkumab was not found to bind to pig cardiac myosin, pig muscle myosin or recombinant human myosin in a further in-vitro binding study. The similar patterns of cross-reactivity exhibited by guselkumab between human and cynomolgus monkey tissues provides further evidence of the pharmacological relevance of this species.

Safety pharmacology programme

A dedicated cardiovascular (CV) safety pharmacology study was undertaken in telemetered cynomolgus monkeys. Central nervous system (CNS) and respiratory safety pharmacology endpoints were assessed as part of the repeat dose toxicology studies following 5 weeks i.v. or s.c. administration.

Cynomolgus monkey was identified as the pharmacologically relevant species to assess the cardiovascular safety of guselkumab. In the pivotal CV safety study, the generation of the statistical analysis summary of the ECG measurements was not GLP compliant; this is not considered to impact on the interpretation of these results. Baseline ECG measurements were taken 5 days prior to dosing i.v. with either 10 or 50 mg/kg of guselkumab. There were no mortalities or adverse clinical

observations following administration. There was a mild (5-12 mmHg) statistically significant decrease in mean arterial blood pressure, and periodic significant decreases in HR with corresponding increased QT interval in the 50 mg/kg group, these changes were small and not considered biologically relevant as they remained within normal range. There was no distribution of guselkumab to cardiac or skeletal muscle detected via immunohistochemistry. The NOAEL for this study was set at the highest dose tested, 50 mg/kg.

CV and respiratory rate in cynomolgus monkeys following administration of guselkumab i.v. up to 5 weeks and s.c. up to 24 weeks at doses of 10 and 50 mg/kg were measured as part of the dose toxicity study. In this study, there was no qualitative change in ECG parameters recorded at any time point or dose level. Statistical analysis of these parameters was not performed. Guselkumab was well tolerated at all doses and routes of administration and the NOAEL was set at 50 mg/kg, the highest dose tested.

CNS related parameters assessed as part of the repeat-dose toxicity study included clinical observations, rectal body temperature and physical examinations of the animals (T-2008-007). There were no significant adverse effects on clinical observations at any dose tested.

Pharmacodynamic drug interactions

No pharmacodynamic interaction studies were conducted. This was considered acceptable by CHMP as no pharmacodynamic interactions are anticipated with co-administered drugs due to the high specificity of guselkumab.

2.3.3. Pharmacokinetics

A single-dose SC and IV study was performed in cynomolgus monkeys to assess PK. Repeat dose TK was evaluated as part of the toxicology studies in guinea pigs and cynomolgus monkeys. Traditional absorption, distribution, metabolism, and excretion studies were not performed. Although the metabolic pathways of therapeutic mAbs are unknown, the expected consequence of metabolism of biotechnology derived mAbs is the catabolism to small peptides and individual amino acids in the same manner as endogenous IgG. Therefore, classical biotransformation studies as performed for small molecule pharmaceuticals are not needed for therapeutic mAbs (ICH S6 [R1]).

Guselkumab concentrations and anti-guselkumab antibodies were analysed from the PK/TK samples that were collected from cynomolgus monkey and guinea pig studies. Validated bioanalytical methods were used to quantify guselkumab concentrations in cynomolgus monkey and guinea pig serum, and in cynomolgus monkey breast milk. Levels of guselkumab in serum and breastmilk or levels of anti-drug antibodies (ADA) against guselkumab in cynomolgous monkey were detected using a DELFIA, an ECLIA or a bridging ELISA respectively. Levels of guselkumab and levels of ADA against guselkumab in guinea pig were detected using a DELFIA and an ECLIA. In general, the bioanalytical methods and assay parameters for the quantitation of guselkumab concentrations and detection of anti-guselkumab antibodies were validated according to criteria established in published literature and validation guidance documents (DeSilva et al., 2003; United States FDA, 2001). These bioanalytical methods evolved as the preclinical development program of guselkumab progressed. All assays are all validated and agreed.

Absorption was studied in the two species used for toxicology assessment, the guinea pig and cynomolgous monkey. In guinea pig, the PK/TK profile was studied in the non-GLP 3 weeks repeated dose toxicity and in male and female fertility studies. In cynomolgous monkey, the PK/TK profile was

studied in the single dose PK study, in the 2 phase repeated dose toxicity study and in the ePPND study. As IL23 is a soluble target, it is expected that pharmacokinetics will follow the normal FcRN mediated degradation pathway of IgG's. Animals were dosed either once (cynomolgous monkey) or twice (guinea pig) a week in contrast to the clinical posology (first two doses 4 weeks apart followed by 8 week intervals). A result of the more frequent dosing interval in animals, up to 2.8 fold accumulation was observed in cynomolgous monkey.

Guselkumab was immunogenic in both guinea pigs and monkeys, as expected for a human mAb. ADA were detected in only 2 (2.2%) of 90 monkeys treated with guselkumab, one after a single 50 mg/kg IV dose of guselkumab and one pregnant female and her infant in the ePPND study receiving 10 mg/kg/week SC guselkumab. One of the monkeys showed accelerated clearance. A higher incidence of ADA was seen after SC doses of guselkumab to guinea pigs, which were administered twice weekly. 83.3% of 66 pregnant and non-pregnant female guinea pigs, 24.7% of 93 male guinea pigs and 19% of 32 pooled foetal samples from guselkumab treated pregnant females were ADA positive. ADA resulted in accelerated decrease of guselkumab serum levels in only a few ADA positive animals, but cynomolgus monkey and guinea pig were sufficiently exposed to observe any potential adverse effects of guselkumab.

As guselkumab is a typical IgG-based mAb (MW 146,613 Da) targeting a soluble target, distribution is assumed to be limited to the vascular space with limited distribution to the extracellular space and the mean volume of distribution was estimated to be dose independent.

Maternal / foetal serum guselkumab ratio was determined at GD30, but since placental transfer of IgG in the guinea pig is not expected to occur before GD30 (reviewed by Pentsuk and Van der Laan, 2009) a conclusion on placental transfer of guselkumab in guinea pig could not be drawn based on the data obtained in the female fertility study.

In the ePPND study, Cynomolgous monkey mean infant/maternal serum concentration ratio, determined at PND28 was 0.83 (50 mg/kg/week). Guselkumab concentrations in PND28 milk samples were below the lowest quantifiable concentration for the assay (i.e., <0.20 µg/mL). This is expected, since limited amount of IgG is only excreted in the first milk of cynomolgous monkey. It can be assumed that distribution to infants have been mainly a result of FcRN mediated placental transfer (reviewed by Pentsuk and Van der Laan, 2009 & Fujimoto K, 1983).

Similar to other IgG1 mAbs, guselkumab is presumably eliminated via catabolic pathways that are typically associated with endogenous IgG. As T1/2 in infant monkeys was slightly higher than in the female (mother) monkeys it is assumed that clearance in infants is slower.

It is unlikely that hepatic cytochrome P450 (CYP)-mediated metabolism represents a major elimination route of guselkumab. In vitro, IL-23 did not alter the expression or activity of multiple CYP enzymes (i.e., 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4) in cryopreserved human hepatocytes, suggesting that potential interactions between guselkumab and CYP substrates are unlikely. Therefore, no nonclinical in vivo drug-drug interaction studies to evaluate the effect of guselkumab on other drugs were conducted, which was considered acceptable by CHMP.

2.3.4. Toxicology

Single dose toxicity

Table 5 - Single dose toxicity and PK study in cynomolgous monkey

Study ID	Species/ Sex/ Number/ Group	Dose/Route	Approx. lethal dose / observe max non-lethal dose	Major findings
P-2007-255 Non-GLP	Cynomolgous monkey 3/group	SC: 1, 10, 50 mg/kg IV: 50 mg/kg 57 days of monitoring	ND	Well tolerated, IV (50): soft stool SC (10 & 50): liquid faeces SC 1-10 mg/kg; ↑ Cmax and AUC less then dose proportionally SC 10-50: mg/kg; ↑ Cmax and AUC dose proportionally

The tolerability of a single dose of guselkumab was assessed in a non-GLP, non-terminal TK/ADA study in male cynomolgus monkeys by the SC (1, 10 and 50 mg/kg) and IV (50 mg/kg) routes of administration (P-2007-255). In addition to the TK and ADA endpoints, body weights and clinical observations were assessed throughout the 57-day study interval. Local tolerance to guselkumab administration was also assessed up to 72-hours post-guselkumab administration. While there were some faecal changes in some animals including a control animal, these were not ascribed to guselkumab administration. There were no signs of guselkumab-related toxicity or effects on local tolerance observed during the conduct of this study.

Table 6 - Mean (SD) Exposure Levels and Antibody Response in Male Monkeys (N = 3) Following a Single IV or SC Dose of Guselkumab

Route	Dose (mg/kg)	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)
IV	50	1363.49 (250.08)	4267.10 (850.47)
SC	1	7.27 (1.88)	113.28 (17.47)
SC	10	48.78 (8.51)	614.26 (117.33)
SC	50	294.37 (21.60)	3357.85 (963.45)

AUC_{inf} = area under the serum concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase; C_{max} = maximum observed serum concentration; IV = intravenous; N = number; SC = subcutaneous; SD = standard deviation

Repeat dose toxicity

A non-GLP 3 weeks repeated dose toxicology study (0, 10, 50 or 100 mg/kg SC biweekly) in Dunkin Hartley Male Guinea Pigs, supported the use of this species for male and female fertility studies. The observed premature mortality and adverse clinical signs noted during the study were considered a result of the primary means of blood collection (i.e., surgically implanted catheters accessing the carotid artery), and thus an alternate collection route (i.e., the jugular vein) was used in subsequent studies.

Table 7 - Mean (SD) Exposure Levels Following the Twice Weekly SC Administration of Guselkumab in a 3-Week Non-GLP Tolerability Study in Guinea Pigs

	TK Following the First Dose on Day 1		TK Following the Last Dose on Day 22		
Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{(0-3d)}$ (µg·day/mL)	C_{max} (µg/mL)	$AUC_{(21-24d)}$ (µg·day/mL)	R[a]
10[b]	62.89 (20.38)[c]	151.41 (40.69)[c]	154.26 (130.63)[d]	401.18 (371.77)[d]	1.18 (0.99)[e]
50[f]	285.17 (21.10)	749.93 (54.84)[g]	878.10 (195.21)	1932.47 (398.88)	2.89 (0.16)[g]
100[f]	693.99 (193.07)	1568.80 (275.21)	1609.59 (478.15)	3977.79 (1285.29)	2.49 (0.41)

[a] The accumulation ratio (R) was calculated by dividing $AUC_{(21-24d)}$ following the last dose on Day 22 (i.e., the seventh dose) by $AUC_{(0-3d)}$ following the first dose on Day 1.
[b] N=4.
[c] N=3 (data from one animal [Animal No. 104] was NR since serum guselkumab concentrations fell below the lowest quantifiable concentration in a sample).
[d] N=3 (one animal was euthanized because of declining condition).
[e] N=2 (one animal was euthanized because of declining condition, and results from another animal [Animal No. 104] were NR since serum guselkumab concentrations fell below the lowest quantifiable concentration in a sample).
[f] N=3.
[g] N=2 (one animal was euthanized because of declining condition).

AUC_{t1-t2} = area under the serum concentration versus time curve from defined time 1 to defined time 2; C_{max} = maximum observed serum concentration; N, No. = number; NR = not reported; R = accumulation ratio; SC = subcutaneous; SD = standard deviation; TK = toxicokinetics

A GLP, 2-phase repeated dose toxicity study was conducted in cynomolgous monkey. Once weekly administration of guselkumab via the IV and SC route for 5 weeks (phase 1) or SC 24 weeks (phase 2) up to 50 mg/kg revealed no toxicity findings at a Cmax more than 200 fold higher and a mean AUCDay 161-168 50-fold higher compared to clinical Cmax and AUCinf levels (single SC dose of 100 mg/k). According to S6R1, toxicity testing of monoclonal antibodies in animals up to 10 fold in excess of human exposure levels is already sufficient.

The applicant has conducted literature search to the role of IL 23 in Coronary artery disease and in immunity towards bacterial and fungal pathogens and combined this knowledge with the non-clinical observations. Preclinical evidence from literature did not support an increased risk of CV events in the setting of IL-23 blockade with guselkumab. In addition, IL-23 may contribute to immunity for a variety of bacterial and fungal pathogens, as assessed in animal models of these infections which has been reported in literature. However, the ability of these models to predict infection risk upon pharmacological IL-23 inhibition in humans has not been established. No direct risk follows from the non-clinical studies.

Toxicokinetics

C_{max} and AUC increased approximately dose proportional. In the 5-weeks study a modest and in the 24-weeks study a moderate accumulation of guselkumab was observed. No antibodies to guselkumab were observed in any animals during the dosing or recovery intervals; therefore, immune response did not affect the TK evaluation. One animal, 10 mg/kg SC Male No. 3003, tested positive for guselkumab antibodies at the Day 1 predose time point. It is unknown what caused this positive result to occur before the dosing period. This animal was negative for guselkumab ADA when measured at D29.

The exposure margin for mean Cmax (992.78 µg/mL) at the NOAEL dose (50 mg/kg/week) was approximately 206.4-fold higher than the mean Cmax in psoriasis patients (4.81 µg/mL) following a single 100 mg/kg SC dose of guselkumab (CNTO1959PSO1001 CSR/Tab 10). The exposure margin for the mean $AUC_{Day\ 161-168}$ value (5411.67 µg.day/mL) in monkeys was approximately 49.9-fold higher than the mean AUC_{inf} value in psoriasis patients following a single 100 mg/kg SC dose of guselkumab (108.48 µg.day/mL). Both provide substantial safety margins.

Table 8 - Summary of Mean Exposure (C_{max} and AUC [SD]) of Guselkumab Following Weekly IV or SC Administration of Guselkumab in a Toxicity Study in Cynomolgus Monkeys (T-2008-007)

TK Parameters[a,b]	Phase 1: 5-Week Administration			Phase 2: 24-Week Administration	
	50 mg/kg IV	10 mg/kg SC	50 mg/kg SC	10 mg/kg SC	50 mg/kg SC
1st Dose (Day 1):					
C_{max} (µg/mL)	1216.05 (178.21)	58.56 (4.31)	322.48 (75.74)	75.57 (12.91)	333.54 (44.65)
$AUC_{Day\ 0-7}$ (µg·day/mL)[c]	2937.21 (438.93)	351.92 (29.89)	1771.48 (281.39)	439.76 (68.62)	1903.28 (202.72)
4th Dose (Day 22):					
C_{max} (µg/mL)	1431.74 (289.90)	127.00 (19.82)	593.41 (150.15)	-	-
$AUC_{Day\ 21-28}$ (µg·day/mL)	4817.17 (1026.92)	747.82 (112.29)	3097.83 (813.80)	-	-
R	1.64 (0.32)	2.13 (0.30)	1.75 (0.34)	-	-
12th Dose (Day 78):					
C_{max} (µg/mL)	-	-	-	171.21 (38.66)	881.85 (122.26)
$AUC_{Day77-84}$ (µg·day/mL)	-	-	-	1011.41 (239.79)	4737.13 (834.85)
R	-	-	-	2.30 (0.41)	2.49 (0.37)
24th Dose (Day 162):					
C_{max} (µg/mL)[c]	-	-	-	167.07 (28.06)	992.78 (62.56)
$AUC_{Day161-168}$ (µg·day/mL)[c]	-	-	-	950.65 (141.98)	5411.67 (444.98)
R[c]	-	-	-	2.27 (0.11)	2.82 (0.39)

[a] The study consisted of 2 phases. In Phase 1, animals (3/sex/group) received IV and/or SC doses once a week for 5 weeks and were euthanized on Day 32. In Phase 2, animals (3 main study animals/sex/group + 2 recovery animals/sex/group) received SC doses once a week for 24 weeks, followed by a 3-month recovery period; main study animals were euthanized on Day 163 and recovery animals were euthanized at the end of the recovery period on Day 247.

[b] Mean values are the average of the mean value for males and females. Mean values shown include all animals, unless noted otherwise.

[c] Values are for 2/sex/group.

AUC_{t1-t2} = area under the serum concentration versus time curve from defined time 1 to defined time 2; C_{max} = maximum observed serum concentration; IV = intravenous; R = accumulation ratio; SC = subcutaneous; SD = standard deviation; TK = toxicokinetics; - = not applicable

Genotoxicity

Genotoxicity studies were not conducted with guselkumab. Genotoxicity studies, routinely conducted for pharmaceuticals, are not applicable to biotechnology-derived pharmaceuticals. Monoclonal antibodies such as guselkumab do not have the same distribution properties as small molecules and are therefore not expected to diffuse across cellular or nuclear membranes and are not expected interact with DNA or other chromosomal material.

The absence of genotoxicity studies to address the mutagenic potential of guselkumab was considered acceptable by CHMP.

Carcinogenicity

Carcinogenicity studies were not performed as guselkumab has species limited cross reactivity that precludes the conduct of traditional rat and mouse bioassays. In the absence of standard carcinogenicity testing in rodents, a weight-of-evidence approach was utilized to determine the potential for carcinogenicity following long-term antagonism of IL-23.

It was concluded that the risk for malignancy associated with long-term inhibition of IL-23 following administration of guselkumab to humans is considered to be low, but it cannot be ruled out as a potential hazard associated with modulation of IL-23 activity.

Reproduction Toxicity

The influence of guselkumab administration on fertility was assessed in female and male Guinea Pigs that were dosed 50 or 100 mg/kg guselkumab subcutaneously twice a week. In the first GLP male fertility study no guselkumab related effects were observed in male animals. However, it appeared that 5/25 of the female littermates from the 100 mg/kg dosed males, underwent complete litter loss. This was not observed in a subsequently conducted mechanistic study or in a second GLP male fertility study, and is therefore not considered treatment-related. Guselkumab was not detectable in the female littermates, suggesting that guselkumab was not transferred during mating. Exposure levels were 24-fold in excess of the clinical exposure levels. In the female fertility study, no guselkumab related effect was noted on female fertility up to exposure levels 12 fold in excess of the clinical exposure levels.

Table 9 - Summary of Mean Exposure (C_{max} and AUC [SD]) of Guselkumab Following Twice Weekly SC Administration of Guselkumab in a Fertility Study in Female Guinea Pigs (T-2011-021)

	Dose (mg/kg)	
	25	
Satellite TK Animals[c]		
	144.71 (17.10)	
	342.64 (75.18)	
	132.11 (57.19)	
	326.64 (163.46)	
	0.97 (0.43)	
Main Study Animals[c]		
	Pregnant	Pooled Foetus
	1.18 (1.75)[e]	<0.04 (NC)[f]
	0.12 (0.13)	

[a] TK parameters shown for treated female guinea pigs from satellite TK and main toxicology study groups.
[b] Mean (SD) values. Mean TK values shown include all animals, unless noted otherwise.
[c] See description above for study design.
[d] The accumulation ratio (R) was calculated by dividing $AUC_{Day\ 32-35}$ following the last dose on Day 32 by $AUC_{Day\ 1-4}$ following the first dose on Day 1.
[e] N=27 (3 animals each from the 25 mg/kg dose group [Animal Nos. 5137, 5148, 5336] and the 100 mg/kg dose group [Animal Nos. 5178, 5184, 5186] were removed from the study). Animal No. 5184 was euthanized on G1D 68 due to adverse clinical observations resembling pregnancy toxemia; the remaining females didn't deliver a litter and were euthanized on G1D 78 (Nos. 5148, 5336, 5178, 5186) or G1D 80 (No. 5137).
[f] N=22 (8 pooled foetal samples each from the 25 mg/kg dose group [Animal Nos. 5135, 5137, 5148, 5140, 5142, 5333, 5334, 5336] and the 100 mg/kg dose group [Animal Nos. 5164, 5165, 5178, 5184, 5186, 5190, 5191, 5338] couldn't be collected as the maternal animals were euthanized prior to delivery, viable conceptuses weren't present, or blood couldn't be collected due to the early gestational age of the foetuses).

AUC_{t1-t2} = area under the serum concentration versus time curve from defined time 1 to defined time 2; C_{max} = maximum observed serum concentration; Conc. = concentration; F = female; GD = Gestation Day; G2D X = GD X of the second gestation period, where "X" is the number of the day; NC = not calculated; No. = number; R = accumulation ratio; SC = subcutaneous; SD = standard deviation; TK = toxicokinetics

Table 10 - Summary of Mean Exposure (C_{max} and AUC [SD]) of Guselkumab Following Twice Weekly SC Administration of Guselkumab in a Fertility Study in Male Guinea Pigs (T-2011-031)

TK Parameters[a]	Dose (mg/kg) 25	100
	Satellite TK Animals[b]	
1st Dose (Day 1):		
C_{max} (µg/mL)	130.72 (22.72)	445.38 (46.62)
$AUC_{Day\ 1-4}$ (µg·day/mL)[c]	327.27 (57.87)[d]	1105.48 (117.01)
13th Dose (Day 43):		
C_{max} (µg/mL)	210.88 (74.16)	1008.63 (139.05)
$AUC_{Day\ 43-46}$ (µg·day/mL)	528.49 (186.74)	2684.49 (351.48)
R[c]	1.55 (0.65)[d]	2.46 (0.45)
19th Dose (Day 64):		
C_{max} (µg/mL)	243.04 (100.57)	1003.93 (103.26)
$AUC_{Day\ 64-67}$ (µg·day/mL)	640.32 (289.43)	2639.13 (228.21)
R[c]	1.93 (1.02)[d]	2.42 (0.38)
	Main Study Animals[b]	
Mean Concentration (µg/mL)	279.84 (125.26)	1550.85 (435.60)

[a] TK parameters shown for treated male guinea pigs from satellite TK and main toxicology study groups.
[b] Satellite groups of guinea pigs (6 M/group) were used for TK and ADA purposes; those animals were dosed twice weekly for a total of 20 doses (i.e., 10 weeks) with the last dose administered on Day 67. The main study (toxicology) animals (25 M/group) were dosed twice a week beginning 7 weeks prior to estimated date of mating, with dosing continuing until a total of 21 doses were administered; the last dose was administered on Day 71, and animals sacrificed on Day 74 or 75.
[c] The accumulation ratio was calculated by dividing either $AUC_{Day\ 43-46}$ following the dose on Day 43 (i.e., the 13th dose) or $AUC_{Day\ 64-67}$ following the dose on Day 67 (i.e., the 20th dose) by $AUC_{Day\ 1-4}$ following the first dose on Day 1, respectively.
[d] N=5 (data from one animal was noted as NA).

ADA = anti-drug antibodies; AUC_{t1-t2} = area under the serum concentration versus time curve from defined time 1 to defined time 2; C_{max} = maximum observed serum concentration; M = male; NC = not calculated; R = accumulation ratio; SC = subcutaneous; SD = standard deviation; TK = toxicokinetics

Table 11 - Summary of Mean Exposure (C_{max} and AUC [SD]) of Guselkumab Following Twice Weekly SC Administration of Guselkumab in a Fertility Study in Male Guinea Pigs (T-2014-021)

TK Parameters[a]	Dose (mg/kg) 100
	Satellite TK Animals[b]
1st Dose (Day 1):	
C_{max} (µg/mL)	511.23 (90.95)
$AUC_{Day\ 1-4}$ (µg·day/mL)	1140.53 (177.26)
13th Dose (Day 43)	
C_{max} (µg/mL)	892.29 (132.07)
$AUC_{Day\ 43-46}$ (µg·day/mL)	2479.10 (373.52)
R[c]	2.22 (0.43)
19th Dose (Day 64):	
C_{max} (µg/mL)	1008.84 (72.38)
$AUC_{Day\ 64-67}$ (µg·day/mL)	2734.39 (172.86)
R[c]	2.46 (0.53)
	Main Study Animals[b]
Mean Concentration (µg/mL)	646.46 (254.69)

[a] TK parameters shown for treated male guinea pigs from satellite TK and main toxicology study groups.
[b] Satellite groups of guinea pigs (6 M/group) were used for TK and ADA purposes; those animals were dosed twice weekly for a total of 20 doses (i.e., 10 weeks) with the last dose administered on Day 67. The main study (toxicology) animals (19 M/group) were dosed twice a week beginning 7 weeks prior to estimated date of mating, with dosing continuing until a total of 21 doses were administered; the last dose was administered on Day 71, and animals sacrificed on Day 72 or 74.
[c] The accumulation ratio was calculated by dividing either $AUC_{Day\ 43-46}$ following the dose on Day 43 (i.e., the 13th dose) or $AUC_{Day\ 64-67}$ following the dose on Day 67 (i.e., the 20th dose) by $AUC_{Day\ 1-4}$ following the first dose on Day 1, respectively.

ADA = anti-drug antibodies; AUC_{t1-t2} = area under the serum concentration versus time curve from defined time 1 to defined time 2; C_{max} = maximum observed serum concentration; M = male; R = accumulation ratio; SC = subcutaneous; SD = standard deviation; TK = toxicokinetics

Embryo foetal development (EFD) and pre and post-natal development (PPND) was evaluated in one ePPND study. Twenty pregnant female cynomolgous monkey were subcutaneously dosed 0, 10 or 50 mg/kg guselkumab once weekly starting from pregnancy day 20-22 up to parturition (GD 160 ±10). Slightly more foetal losses occurred in the guselkumab treated females. Also slightly more infant losses occurred in guselkumab females. Number of surviving infants was within likely outcomes for a NHP ePPND study (Jarvis et al., 2010) for all groups. Cmax and AUC increased approximately dose proportional. Guselkumab was quantifiable in mothers up to 91 days postpartum (last dose). ADA was

measured in 1/40 mothers and also in her infant. The serum guselkumab ratio for infant/mother was 0.7 for 10 mg/kg dosed females and 0.83 for 50 mg/kg dosed females. Again, dosing was quite in excess to the requirements of S6R1, which recalls that an animal exposure 10 fold in excess of human exposure levels is already sufficient.

Toxicokinetics

During Gestation

The Cmax and the AUC within 1 dose interval increased in an approximately dose-proportional manner in the dose range from 10 to 50 mg/kg following weekly SC administrations of guselkumab to pregnant monkeys. Steady state was reached by GD91 following weekly SC administrations of guselkumab to pregnant monkeys. Moderate drug accumulation occurred in the pregnant monkeys' systemic circulation when guselkumab was administered SC once every week. Quantifiable concentrations were observed up to 91 days post parturition for most maternal and infant animals.

In the Postnatal Period

The mean T1/2 of guselkumab was relatively consistent between the 10 and 50 mg/kg/week dose groups in maternal and infant animals. The mean T1/2 of guselkumab in the infants was slightly longer than the one in the maternal animals. Guselkumab concentrations were below the lowest quantifiable concentration in the milk samples on postpartum day (PND) 28, which is expected since IgG are only very limited excreted in the first milk. Significant guselkumab concentrations were observed in the serum samples at the same time point. Guselkumab concentrations in the infants were similar to the ones in the maternal animals on PPD28.

Anti-Drug Antibodies

One out of 40 maternal animals and its infant from the guselkumab treated groups tested ADA positive (Adult Female No. 2512 and Infant No. 2121, 10 mg/kg/week). The mother exhibited an accelerated decrease in guselkumab concentrations starting from the time point on GD56. Serum guselkumab concentrations in all collected samples from the infant were below the lowest quantifiable concentration. Two control infants (Infant Nos. 1161 and 1186) tested ADA positive for unknown reasons; both maternal females (Adult Female Nos. 1516 and 1518, respectively) were negative for ADA.

Table 12 - Guselkumab ePPND Study: Infant Losses

Group	Dose Level (mg/kg/week)	Total No. Infants	Delivery Day[a]	Day of Death	Comment
1	0	16	GD 161	BD 5*	Maternal neglect BD 1; unsuccessful attempt to cross foster infant to adult females; infant euthanized
2	10	14	GD 171	BD 1*	Live birth GD 171; infant found dead, possibly related to maternal neglect.
			GD163	BD 7	Infant weak/pale at BD 7 evaluations, not nursing, required euthanasia. Infection secondary to tail injury.
			GD 147	BD 2*	Preterm birth. Infant found dead; mouth laceration / probable effect on nursing.
3	50	14	GD 143[b]	BD 1*	Preterm birth GD 143; infant died.
			GD 173	BD 6	Infant found dead. Demise possibly related to episodic nursing pattern of the infant. Unknown relationship if any to the late term birth.
			GD 134	BD 1*	Premature birth; evidence of maternal neglect; infant euthanized.

[a] Deliveries that occurred prior to GD 140 were considered premature, since infants born on GD 140 or later can be expected to survive. Those that occurred prior to GD 152 were considered preterm and those that occurred after GD 166 were considered late term (based on historical control data for average gestation length of 159 ± 7 days for 16 ePPND studies conducted at the Testing Facility from 2008 to 2013, inclusive).

[b] Only female with infant loss on the present study that had known parity from a previous ePPND study.

BD = Birth Day; ePPND = enhanced pre- and postnatal development; EU = euthanized; FD = found dead; GD = Gestation Day; No. = number; * = potentially attributable to maternal neglect, injury or trauma; - = not applicable;

Local Tolerance

Separate studies assessing the local tolerability of guselkumab have not been conducted. Reactions at the injection site were evaluated in guinea pigs administered twice weekly SC doses of up to 100 mg/kg guselkumab, and in single dose, repeat dose, and ePPND studies in which cynomolgus monkeys received weekly IV and SC doses of up to 50 mg/kg guselkumab. All findings were considered to be related to the dosing procedure and not to treatment with guselkumab.

Local tolerance has been addressed in the repeated dose toxicity and the reprotoxicity studies. No guselkumab related effects were found. The absence of dedicated local tolerance studies is considered acceptable by CHMP.

Other toxicity studies

Immunotoxicity has been sufficiently addressed in the repeated dose toxicology and the ePPND study in monkeys. Cellular distribution of T and B cells was examined on H&E stained lymphoid tissues (spleen, thymus, lymph nodes (axillary, inguinal, mandibular, and mesenteric) Peyer's patch and tonsil) were stained using specific antibodies towards T and B cells. Hematology, immunophenotyping via flow cytometry, and TDAR to KLH were also assessed. In the ePPND study hematology, immunophenotyping, and TDAR to KLH were assessed in females and their infants. Lymphoid tissues from infants were examined microscopically and IHC was performed for CD3/CD20 cell subsets. Guselkumab treatment had no effect on hematology, immunophenotyping, TDAR to KLH, histopathology of immune tissues, or T- and B-cell distribution in monkeys or their offspring.

Tissue cross reactivity of guselkumab was tested on a series of 35 human tissues from 3 subjects and 32 cynomolgous monkey tissues in a non-GLP and a GLP TCR study. Besides the expected guselkumab staining of macrophages, dendritic cells, keratinocytes and low grade neural staining, unusual cardiomyocyte staining was observed. This preceded the conduct of the CV safety pharmacology study in cynomolgus monkeys, in which besides CV endpoints, tissues were collected from some animals and evaluated by IHC at the same laboratory that conducted the non-GLP and GLP

TCR studies. These indicated that the cytoplasmic binding observed during in TCR studies is likely not relevant to in vivo studies. Absence of adverse CV effects and lack of heart and muscle pathology in guselkumab treated cynomolgus monkey in CV safety pharmacology study and in the GLP 5 week/24-week study, further supported the lack of guselkumab related CV effects in monkeys.

Serum Compatibility and Haemolytic Potential of Guselkumab was assessed in an in vitro assays using human serum and human whole blood from a human volunteer. No precipitation or coagulation was observed when guselkumab was co incubated with human serum, and no signs of haemolysis were observed following the co incubation of guselkumab with human whole blood. In short, results indicated that guselkumab was compatible in serum and exhibited no haemolytic potential at concentrations up to 65 mg/mL

Further studies addressing toxicity of guselkumab in juvenile animals, in addition to the ePPND study, were not conducted, which was considered acceptable by CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

Guselkumab is a newly developed human anti-IL23p19 antibody that targets psoriasis, an autoimmune dermatological disease. From the assumed mechanism of action guselkumab might be efficient in reducing the symptoms of psoriasis. A thorough preclinical study program has been conducted. Primary pharmacodynamic studies characterized guselkumab in terms of its binding interactions, mechanism of action, functional effects of neutralization, species cross-reactivity, and in vivo activity supporting a psoriasis indication.

The non-clinical studies adequately provide evidence that guselkumab neutralizes human IL-23 with high affinity and specificity and consequently inhibits the immune response by Th17 lymphocytes.

Human IL-23 seemed to increase serum levels of several cytokines in mice. Intraperitoneal (i.p.) administration of both recombinant mouse (rm) IL-23 and rhIL-23 to C57BL/6 mice was found to result in dose dependent increases in serum levels of IL- 1α, G-CSF, IP-10, TNFα, GM-CSF and MCP-1. Guselkumab administration was shown to attenuate rhIL-23 induced increases in serum levels of cytokines IL- 1α and G-CSF without any significant change in TNFα, IP-10 or GM-CSF levels. The low number of study animals and the high deviations of the data prevent to draw a firm conclusion. It was stated that it was not possible to measure IL-17A production (IL-17F was not measured at all) induced by hIL-23, which impairs the interpretation of the data. Overall, this animal model of testing the effectiveness of hIL-23 and consequently the inhibitory capability of guselkumab is of limited value. It is accepted that no nonclinical model of plaque psoriasis that recapitulates all facets of human psoriasis is available. From an efficacy point of view human studies may provide more robust evidence of the therapeutic value of guselkumab.

In vivo secondary pharmacodynamic and pharmacodynamic interactions studies have not been conducted. This approach is acceptable as guselkumab is highly specific and no other binding targets

are expected. Similarly, no other specific IL-23 antagonists, - except ustekinumab, that is an IL-12 and IL-23 antagonist – is known, therefore it is unlikely to have pharmacodynamic interactions with co-administered drugs.

Secondary pharmacological in vitro studies investigated the tissue cross-reactivity of guselkumab. Guselkumab was not found to bind to pig cardiac myosin, pig muscle myosin or recombinant human myosin in a further in-vitro binding study. The similar patterns of cross-reactivity exhibited by guselkumab between human and cynomolgus monkey tissues provides further evidence of the pharmacological relevance of this species. It would seem that the cytoplasmic staining of myocytes is not relevant to in-vivo administration as the antibodies are too big to cross cellular membrane. The lack of myocyte staining associated with unconjugated guselkumab administration reported in the CV safety pharmacology study further corroborates this.

In safety and toxicological studies no significant treatment related adverse effects on cardiovascular, respiratory and CNS functions were revealed.

As IL23 is a soluble target, it is expected that pharmacokinetics will follow the normal FcRN mediated degradation pathway of IgG's, also apparent from a dose proportional increase in C_{max} and AUC. Animals were dosed either once (cynomolgous monkey) or twice (guinea pig) a week in contrast to the clinical posology (first two doses 4 weeks apart followed by 8 week intervals). A result of the more frequent dosing interval in animals, up to 2.8 fold accumulation was observed in cynomolgous monkey.

No toxicity was observed in cynomolgous monkey that were exposed to guselkumab 50-fold in excess of clinical levels, except for a transient, statistically significant reduction in IgM titers observed in the high dose group. No corresponding effects on IgG levels were observed, and no guselkumab related infections were identified in any of the toxicity studies conducted. Also the margin of safety (8 fold in terms of AUC, 34 fold in terms of Cmax) between exposure levels at the lower dose level (10 mg s.c. qw) tested in the repeat dose cynomolgus toxicity study (at which animals did not exhibit any signs of immunosuppression) and reported human exposures following a single 100 mg s.c. dose to psoriatic patients is reasonable. Therefore it can be anticipated that guselkumab will not functionally affect host immunity.

The applicant has conducted a literature search to the role of IL 23 in Coronary artery disease and in immunity towards bacterial and fungal pathogens and combined this knowledge with the non-clinical observations. Preclinical evidence from literature did not support an increased risk of CV events in the setting of IL-23 blockade with guselkumab. In addition, IL-23 may contribute to immunity for a variety of bacterial and fungal pathogens, as assessed in animal models of these infections which has been reported in literature. However, the ability of these models to predict infection risk upon pharmacological IL-23 inhibition in humans has not been established. No direct risk follows from the non-clinical studies.

No carcinogenicity studies were performed and as such, a weight of evidence approached was used. It was concluded that the risk of malignancy associated with long-term inhibition of IL-23 following administration of guselkumab to humans is considered to be low, but it cannot be completely ruled out as a potential hazard associated with modulation of IL-23 activity. Malignancies has been included has an important potential risk in the RMP. Also malignancies in humans will be monitored during clinical trials and in post-marketing.

In the ePPND study in monkeys, an increase in fetal and infant deaths were observed in the treated groups. (3/19 fetal deaths were found in control group versus 12/40 in treated monkeys. 4/19 fetal and infant deaths were found in control group versus 18/40 in the treated monkeys. Convincing arguments that all embryo/foetal and neonatal deaths were within the range of historical control data

were provided. The information with regard to the causes of death does not point towards a relation to guselkumab treatment. Furthermore, data from literature indicate that IL-23 deficient mice (IL-23p19-/-) are normal in size and fully fertile. Instead, transgenic mice with widespread expression of p19 showed systemic inflammation, infertility, impaired growth, and premature death. In humans, knowledge on the role of IL-23 in pregnancy and potential role in spontaneous recurrent abortions is emerging and rather indicative for an improvement of pregnancy maintenance upon inhibition of IL-23. Also from literature, a relation to IL-23 inhibition and increase of number of abortions is thus not likely.

A conclusion on placental transfer of guselkumab in guinea pig could not be drawn based on the data obtained in the female fertility study, since determination of maternal / foetal serum guselkumab ratio was done at GD30 when placental transfer is not yet expected in the guinea pig (reviewed by Pentsuk and Van der Laan, 2009). In the ePPND study, guselkumab distribution to infants have been mainly a result of FcRN mediated placental transfer as IgGs, like guselkumab, are only poorly excreted in the first milk of cynomolgous monkeys (reviewed by Pentsuk and Van der Laan, 2009 & Fujimoto K, 1983). Plasma exposure to guselkumab was similar in the pups and the dam.

The development of the immune system occurs in the first trimester of pregnancy and training of the immune system after birth. The transplacental exposure to guselkumab of infant monkeys occurs in the third trimester of pregnancy and will not likely disturb development. Thereby, analyses of the immune system by histopathology and also by functional testing in these monkeys do not indicate impaired function of the immune system. It seems that the immune system is functional in in-utero exposed monkey infants and it can be anticipated that a functional response to immunisation will not be disturbed either. However, the applicant notes that guidance with regard to vaccinations to in-utero guselkumab exposure should be nationally regulated. This is considered acceptable by CHMP.

Local tolerance of the proposed clinical formulation was adequately addressed as part of the ePPND study (T-2012-019), which is acceptable and in line with the ICH S6 (R1) guideline.

2.3.7. Conclusion on the non-clinical aspects

The IL-23 neutralizing capability, specificity and the inhibition of the downstream production of IL-17 by guselkumab have been satisfactorily demonstrated through non-clinical pharmacodynamics studies. The primary pharmacodynamic studies are sufficient and the lack of secondary and pharmacodynamics interaction studies is acceptable due to the high specificity of guselkumab.

In ePPND study in cynomolgous monkeys although numerically higher, fetal losses fall within the variable historical control data. Applicant discussed literature data on IL-23 during pregnancy, suggesting positive correlation between spontaneous abortions and IL-23 levels and limited human in vitro data are suggesting similar correlations.
In utero exposure and functional consequences of that are included in the RMP as missing information. Histopathological and functional analyses in transplacentally exposed monkeys do not indicate impaired function of the immune system and it can be anticipated that a functional response to childhood vaccinations will not be disturbed either.
Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28. However, as it is unknown whether guselkumab is excreted in human milk precautionary statements about breast feeding have been added to the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

The efficacy of guselkumab in the treatment of moderate to severe plaque psoriasis in adults is supported by analyses from 6 core psoriasis studies:

- Two Phase 1 studies:

  CNTO1959PSO1001 (referred to as PSO1001)

  CNTO1959PSO1002 (referred to as PSO1002)

- One Phase 2 study:

  CNTO1959PSO2001 (X-PLORE, PSO2001)

- Three Phase 3 studies:

  CNTO1959PSO3001 (VOYAGE 1, PSO3001)

  CNTO1959PSO3002 (VOYAGE 2, PSO3002)

  CNTO1959PSO3003 (NAVIGATE, PSO3003)

The safety of guselkumab was evaluated primarily in the psoriasis population in a total of 1,748 subjects with moderate to severe plaque psoriasis treated in studies PSO2001, PSO3001, PSO3002, and PSO3003. In the analysis of the Phase 3 safety data from studies PSO3001 and PSO3002, 1,367 subjects included in the primary analysis data set received the proposed guselkumab dose regimen of 100 mg, administered SC, at Weeks 0 and 4 and then q8w thereafter, including 592 subjects treated for 48 weeks (1 year). The size of this safety database is sufficient to provide a robust evaluation of the safety of guselkumab in the target population.

In addition to the 6 core psoriasis studies, 4 completed (CNTO1959NAP1001, CNT01959NAP1002, CNTO1275ARA2001, CNTO1959PPP2001) and 5 ongoing studies (CNTO1959PSO1003, CNTO1959PSA2001, CNTO1959PPP3001, CNTO1959PSO3004, CNTO1959PSO3005) with guselkumab in other indications (PPP, PsA), other populations (eg, from Japan only), or to investigate drug-drug interactions (study CNTO1959PSO1003), provide supportive safety and/or pharmacokinetic (PK) and immunogenicity information in this submission.

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 13 - Clinical Studies Supporting the Efficacy of Guselkumab in Subjects with Plaque Psoriasis

Study	Description	Treatments	Key Results/ Primary and Major Secondary Endpoints
Phase 1: Randomized, double-blind, placebo-controlled, ascending single-dose study			
PSO1001	- Healthy adults Part 1, *16 Wk* - Target population Part 2, *24 Wk*	- Part 1: 0.03, 0.1, 0.3, 1, 3, 10 mg/kg IV or 3 mg/kg SC guselkumab or placebo (n=47) - Part 2: 10, 30, 100, 300 mg SC guselkumab or placebo (n=24)	Key results: acceptable safety in both populations; data on the magnitude and duration of efficacy following single doses
PSO1002	Japanese target population *24 Wk*	10, 30, 100, or 300 mg SC guselkumab or placebo (n=24)	Comparable results to those from Part 2 of study PSO1001
Phase 2: Dose-range finding, placebo-controlled, active-controlled study			
PSO2001 (X-PLORE)	Dose range finding, efficacy and safety in target population *52 Wk*	- Placebo SC, Wk0, 4, 8 (n=42), crossover guselkumab 100 mg, Wk16, q8w (n=39) - Guselkumab SC 5 mg, 50 mg, 200 mg, Wk0, q12w (n=41) - Guselkumab SC 15 mg, 100 mg, Wk0, q8w (n=41) - Adalimumab SC 80 mg Wk0, 40 mg Wk1, q2w (n=43)	Key results: the 100 mg q8w dose regimen had the best efficacy among all dose regimens studied. Dose regimens lower than 100 mg q8w were consistently less effective and the dose regimen of 200 mg q12w did not provide incremental benefit over 100 mg q8w
Phase 3: Placebo-controlled, active-controlled study			
PSO3001 (VOYAGE 1)	Efficacy and safety in target population 160 Wk Wk 48 DBL Study Ongoing	- Guselkumab SC 100 mg, Wk0, 4, q8w (n=329) - Placebo SC starting Wk0, guselkumab SC 100 mg, Wk16, 20, q8w (n=174) - Adalimumab SC 80 mg Wk0, 40 mg Wk1, q2w (n=334)	Primary and Major Secondary Endpoints: - Wk16: PASI 75, 90, IGA 0/1, ss-IGA 0/1, DLQI & PSSD change from baseline. - WK24: IGA 0, 0/1, PASI 90, PSSD symptom score 0 - WK48: IGA 0, 0/1, PASI 90 - Superiority to placebo and adalimumab in a pre-specified hierarchical analysis
PSO3002 (VOYAGE 2)	Efficacy and safety in target population 160 Wk - Wk 48 DBL - Study Ongoing	- Guselkumab SC 100 mg, Wk0, 4, 12, 20 (n=496) - Placebo SC starting Wk 0, guselkumab SC 100 mg, Wk16, 20 (n=248) - Adalimumab SC 80 mg Wk 0, 40 mg Wk1 to 23 (q2w) (n=248) Starting Wk28, therapy for all subjects based on their initial treatment group assignment and their level of response at that visit	Primary and Major Secondary Endpoints: - Wk16 and Wk24: endpoints as in study PSO3001 - Wk28-48: time to loss of PASI 90 response - Superiority to placebo and adalimumab in a pre-specified hierarchical analysis
Phase 3: Active-controlled study			
PSO3003 (NAVIGATE)	Efficacy and safety in target population with an inadequate response to ustekinumab 60 Wk - Wk 40 DBL - Study Ongoing	Ustekinumab SC 45mg or 90mg, Wk0, 4 (n=871) At Wk16: Ustekinumab inadequate responders (IGA ≥2): - Guselkumab SC 100 mg, Wk16, 20, q8w (n=135) - Ustekinumab SC 45 mg or 90 mg, q12w (n=133) Ustekinumab responders (IGA 0/1) (n=585): - Ustekinumab SC 45 mg or 90 mg, q12w All subjects: post treatment follow up Wk48 to 60	Primary and Major Secondary Endpoints: - Wk28 through Wk40: Number of visits at which subjects achieved a IGA 0/1 and ≥2-grade improvement (relative to Wk16), a PASI 90 response or an IGA 0. - Proportion of subjects with IGA 0/1 and ≥2-grade improvement (relative to Wk16) at Wk28

PASI=Psoriasis Area and Severity Index; IGA=Investigator's Global Assessment; ss-IGA= scalp-specific IGA;, DLQI=Dermatology Life Quality Index; PSSD=Psoriasis Symptom and Sign Diary; DBL=database lock

2.4.2. Pharmacokinetics

The core psoriasis clinical development program of guselkumab consisted of two Phase 1, one Phase 2, and three Phase 3 studies. The single dose studies were carried out in healthy volunteers and psoriasis patients, while the multiple dose studies were carried out in psoriasis patients.

A lyophilized formulation was used for early Phase 1 and 2 studies (PSO1001, PSO1002, PSO2001, ARA2001, and PPP2001), and a liquid formulation in a prefilled syringe (PFS-U) was used later on. The product to be marketed is the liquid formulation (PFS-U) and this was used in all Phase 3 studies.

Analytical methods

Guselkumab concentrations

Two methods were developed for the determination of serum guselkumab concentrations. A validated dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) method was used to determine

serum guselkumab concentrations for samples in early Phase 1 and Phase 2 studies, including PSO1001, PSO1002, and PSO2001. An electrochemiluminescent immunoassay (ECLIA) method was later developed and validated for the measurement of serum guselkumab concentrations in the Phase 3 studies including PSO3001, PSO3002, and PSO3003. Serum samples from the Phase 2 PSO2001 study were initially analysed using the DELFIA method but were subsequently reanalysed using the ECLIA method. Both assays displayed acceptable precision, accuracy, dilution linearity, sample stability and the assays have been cross-validated. The sensitivity of the DEFLIA method was 40 ng/ml and the ECLIA method had a slightly better sensitivity of 10 ng/ml.

Determination of Antibodies to Guselkumab

The bioanalytical method for ADA determination is a non-quantitative, titer-based bridging ECL-based immunoassay. The presence of ADA was evaluated using the recommended three tiered approach: an initial screening assay to identify potentially ADA positive samples, a confirmation (specificity) assay based on competition with exogenously added guselkumab, and a determination of the titer of ADA for confirmed positive samples.

Assay for the determination of neutralising antibodies to guselkumab

A neutralising antibody (Nab) was developed based on a reduction in signal when NAb compete with Ruthenium labelled IL-23 for binding to guselkumab. The cut point of the assay was estimated using serum samples form psoriasis and rheumatoid arthritis patients. The assay displayed acceptable precision, robustness and sample stability. The sensitivity of the assay was shown to 157.5 ng/mL in neat human serum and the assay could tolerate a maximum of 0.83 µg/mL of guselkumab.

Absorption

Guselkumab was slowly absorbed into the systemic circulation with median time to reach the maximum serum concentration (Tmax) values of approximately 3.2 to 6.0 days after single subcutaneous (SC) administration at doses ranging from 10 mg to 300 mg in subjects with psoriasis, and 5.0 to 5.5 days after a single 100-mg SC administration in healthy subjects.

The mean absolute bioavailability (F) of guselkumab following a single 100-mg SC administration was estimated to be approximately 47.6% and 48.7% for lyophilized formulation and the liquid formulation in PFS-U. By comparison to other mABs the absolute bioavailability of the product to be marketed is at the lower end of the spectrum.

Bioequivalence

A phase 1 PK comparability study in healthy subjects (NAP1001) demonstrated satisfactory PK comparability of guselkumab between the lyophilized formulation and the liquid formulation. The systemic exposures (Cmax and AUCs) of guselkumab were comparable between the liquid formulation (supplied as PFS-U) and the lyophilized formulation: the geometric mean ratios of the Cmax and AUCs were close to 1 (0.96-0.99) and the 90% Cis of the geometric mean ratios were all within the interval of 0.80-1.25.

Distribution

The mean volume of distribution based on the terminal phase (Vz) values observed following a single IV administration in healthy subjects was approximately 6.7 to 10.1 L (98 to 123 mL/kg), suggesting that guselkumab is primarily confined in the circulatory system with limited extravascular tissue

distribution. Following a single SC administration, the mean Vz/F values were approximately 16.1 to 28.0 L (177 to 288 mL/kg) in subjects with psoriasis (PSO1001 Part 2 and PSO1002) and 12.9 to 16.6 L (191 to 241 mL/kg) in healthy subjects (NAP1001).

Elimination

The mean T1/2 values ranged from approximately 12.3 to 19.1 days after a single IV administration in healthy subjects (NAP1001, PSO1001 Part 1) and approximately 14.7 to 17.6 days after a single SC administration in subjects with psoriasis (PSO1001 Part 2 and PSO1002). The mean T1/2 value was approximately 17 days (ranged from approximately 16.6 to 17.2 days) after a single 100-mg SC administration in healthy subjects (NAP1001).

The mean CL values following a single IV administration in healthy subjects were approximately 0.299 to 0.479 L/day (3.6 to 6.0 mL/day/kg, PSO1001 Part 1) and 0.288 L/day (4.2 mL/day/kg, NAP1001). The mean apparent total systemic clearance (CL/F) values following a single SC administration ranged from approximately 0.677 to 1.278 L/day (7.5 to 13.9 mL/day/kg) in subjects with psoriasis (PSO1001 Part 2 and PSO1002) and 0.531 to 0.681 L/day (7.8 to 9.9 mL/day/kg) in healthy subjects (NAP1001). Given an absolute bioavailability of approximately 50%, these CL/F values are generally consistent with the CL values reported in the IV studies (PSO1001 Part 1 and NAP1001). The CL/F values were somewhat higher in subjects with psoriasis (N=3 to 5 subjects per group).

These findings of higher CL/F values in subjects with psoriasis may be attributed to a variety of factors including small sample size in Phase 1 studies in subjects with psoriasis, inter-study and/or inter-subject variability, or differences in weight between the study populations. Because the kinetics was linear and time independent it might be assumed that guselkumab is eliminated via a large-capacity nonspecific IgG elimination pathway and the specific target-mediated drug disposition (TMDD) pathway does not have a role.

Dose proportionality and time dependencies

The systemic exposure (maximum observed concentration [Cmax] and area under the concentration versus time curve [AUC]) increased in an approximately dose-proportional manner after single intravenous (IV) administration at doses ranging from 0.03 to 10 mg/kg (ie, approximately 2.7 mg to 900 mg for a subject weighing 90 kg) or after a single SC administration at doses ranging from 10 mg to 300 mg.

Guselkumab exhibited linear PK following multiple SC administrations at dose levels ranging from 15 to 200 mg (Study PSO2001). Serum guselkumab concentrations achieved steady state approximately by Week 16 for all dose groups randomized to guselkumab. In each treatment group, mean or median trough serum guselkumab concentrations were maintained at steady state through Week 52. There was no evidence of substantial accumulation in serum guselkumab concentrations over time.

It is noted that dose proportionality is not apparent when comparing mean or median serum concentrations from Week 4 through Week 52 between the 5 mg q12w group and the 50 mg or 200 mg q12w groups. A possible and reasonable explanation of this finding is that the 5 mg q12w group 30.6% of subjects at Week 16 had concentrations below BLQ.

Special populations

No pharmacokinetic studies have been conducted in special populations (i.e., paediatric [<18 years of age], elderly, subjects with renal or hepatic impairment). Results from population PK analyses indicate that age (>65 years versus <65 years), or baseline laboratory measurements (alkaline phosphatase and estimated serum creatinine clearance) did not have a clinically relevant effect on the CL/F of guselkumab.

The lack of PK studies in special patient groups was found acceptable on the ground that guselkumab pharmacokinetics shows the general features of other IgG based mABs and previous regulatory and therapeutic experiences with these drugs do not warrant these studies.

Population Pharmacokinetic Analysis

The serum guselkumab concentration data collected from the Phase 2 dose-ranging study (PSO2001 through Week 40) and 2 Phase 3 studies (PSO3001 through Week 44 and PSO3002 through Week 48) were utilized to perform a population PK analysis using nonlinear mixed-effect modelling approach. A total of 13,014 serum samples were included in the population PK analysis. A one-compartment PK model with first-order absorption and first-order elimination was selected as the structural PK model to describe the serum concentration versus time profiles of guselkumab following SC injections in subjects with psoriasis.

Standard diagnostic plots were generated to evaluate the adequacy of the base and final covariate models. Among the intrinsic and extrinsic factors evaluated, comorbidity of diabetes, and race (non-Caucasian versus Caucasian) had marginal effects on CL/F (12% and 11%, respectively) while the influence of body weight on CL/F and Vd/F were are greater than 20%. Note that Cl/F and Vd/F are positively correlated with each-other and they are negatively correlated with AUCt and Ctroughss. Thus, the effects of body weight on concentration via these two PK parameters are additive but still moderate. The model-predicted median steady-state trough concentration and AUCt of guselkumab in patients subjects with a body weight > 90 kg were about 34% and 29% lower than in subjects < 90 kg, respectively, at 100 mg q8w.

Population PK/PD modelling

For exposure-response modelling analyses for efficacy, two complementary modelling approaches were used to characterize the exposure-response relationships in subjects with psoriasis:

1) a landmark analysis approach using ordinal logistic regression to link the IGA and PASI outcomes at Week 16 and Week 28 to the exposure parameters of model-predicted individual trough serum guselkumab concentration and AUC; and

2) a longitudinal modelling approach employing a mechanism based indirect response (IDR) model to characterize the time-course of the IGA and PASI outcomes.

Both models adequately described the concentration and time dependence of the therapeutic outcomes. The parameter estimates applied imply that heavier subjects expect slower improvement and less sensitivity to treatment. To justify the dose selection, simulations were conducted for the proportions of subjects achieving IGA 0/1, IGA 0, PASI 75, PASI 90, and PASI 100 response rates for the dose levels up to 200 mg under the same q8w dose regimen as in the PSO3001 and PSO3002 studies. The simulations suggest that the 100-mg q8w dose regimen resulted in systemic exposures that provide high efficacy approaching the plateau of the dose-response curve for the overall population.

Effect of Antibodies to Guselkumab on Pharmacokinetics

Seventy-nine of 1,454 (5.4%) subjects who were positive for antibodies to guselkumab were included in the population PK analysis. In the population PK covariate analysis, the presence of antibodies to guselkumab did not have an apparent impact on PK exposure of guselkumab when comparing the CL/F values between subjects who were positive for antibodies to guselkumab and subjects who were negative for antibodies to guselkumab In a separate sensitivity analysis using the final model, the impact of antibodies to guselkumab as a time-varying variable did not have an apparent effect on CL/F of guselkumab. However, due to the low incidence of antibodies to guselkumab, the result should be interpreted with caution.

Mean and median serum guselkumab concentrations in subjects positive for antibodies to guselkumab were generally similar compared with those who were negative for antibodies to guselkumab in studies PSO2001, PSO3001, PSO3002, and PSO3003. In addition, no apparent impact of the peak titer levels of antibodies to guselkumab on the PK of guselkumab was observed in subjects positive for antibodies to guselkumab.

Pharmacokinetic interaction studies

An in vitro study showed that IL-23 did not alter the expression or activity of multiple cytochrome (CYP) P450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4), which suggested that therapeutic protein-drug interactions between guselkumab and CYP substrates are unlikely. A Phase 1 clinical study (PSO1003) was conducted in subjects with moderate to severe psoriasis to evaluate if blocking IL-23 with guselkumab for treatment of psoriasis will alter the metabolism of probe substrates metabolized by CYP450 isozymes.

Study CNTO1959PSO1003 was an open-label, multicenter, Phase 1 drug interaction study designed to evaluate the effect of a single SC dose of 200 mg guselkumab on the PK of a cocktail of representative probe substrates of CYP isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]).

A total of 17 subjects with psoriasis were enrolled into the study, of which 16 subjects received at least 1 probe cocktail administration and 14 subjects received treatment with guselkumab. Of the 16 subjects who received study agents (either probe cocktail or guselkumab), 12 subjects completed the study.

All subjects were to receive a single SC dose of 200 mg guselkumab on Day 8. All subjects were to receive a probe cocktail administration on Days 1, 15, and 36. The probe cocktail consisted of oral doses of 0.03 mg/kg of midazolam, 10 mg of warfarin (+10 mg of vitamin K), 20 mg of omeprazole, 30 mg of dextromethorphan, and 100 mg of caffeine.

Blood samples were collected for the measurement of plasma concentration of CYP probe substrates including midazolam, omeprazole, S-warfarin, dextromethorphan and caffeine. PK parameters for midazolam, omeprazole, S-warfarin, dextromethorphan and caffeine were calculated from plasma concentration-time data using non-compartmental analyses.

PK parameters were calculated from plasma concentration-time data using non-compartmental analyses. PK parameters included, but were not limited to, maximum observed plasma concentration (Cmax) and the area under the concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase (AUCinf). The interaction effect was assessed by computing the geometric mean ratios and associated confidence intervals of the PK parameters measured at Day15 and Day 36 versus Day 1. In none of the cases was the point estimate above 2 which would indicate a clinically significant interaction. The upper confidence limits were above 2 in the case of

dextromethorphan, but this is due to the large inter-subject variability. Results of study PSO1003 suggest that the metabolic activities of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 were not affected by the decreased inflammation associated with the improvement of disease activity in subjects with psoriasis.

Relationship between plasma concentration and safety

The proportions of subjects who had AEs, SAEs, infections, infections requiring treatment, and AEs leading to discontinuation through Week 28 were evaluated with respect to observed steady-state trough serum guselkumab concentration levels at Week 28. In general, the occurrence of selected safety events was not associated with serum guselkumab concentrations. This was evidenced by the proportions of subjects who had treatment-emergent AEs, SAEs, infections, infections requiring antimicrobial treatment, or AEs leading to discontinuation that were not increased consistently with increasing steady-state trough serum guselkumab concentrations . Although subjects who had serum guselkumab concentrations at the fourth quartile level had 12-13% higher rates of infections when compared with subjects who had serum guselkumab concentrations in the lower three quartiles, the clinical relevance of this finding appears to be limited, given that the vast majority of infections was non-serious and mild to moderate in intensity and that the frequency of the infections requiring treatment was generally similar across all four exposure quartiles. The number of subjects who discontinued the treatment due to adverse events is minimal and does not show exposure dependency.

2.4.3. Pharmacodynamics

Mechanism of action

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

Primary and Secondary pharmacology

Biomarkers were assessed in three clinical studies including one Phase 1 (CNTO1959PSO1001), one Phase 2 (CNTO1959PSO2001) and one Phase 3 (CNTO1959PSO3001) study.

In PSO1001, histologic analysis and gene expression profiles of skin biopsy specimens obtained from guselkumab-treated subjects were compared with those obtained from placebo treated subjects. Skin biopsy specimens were collected before initiation of treatment (baseline) and at Weeks 1 and 12.

Treatment with guselkumab resulted in improvement in histological measures of psoriasis at Week 12 including reductions in epidermal thickness, T-cell density, and dendritic cells. At baseline, increases in T-cell counts (CD3), myeloid dendritic cell (DC) counts (CD11c), and epidermal hyperplasia and KRT16 were observed in lesional skin compared with values in nonlesional skin. At Week 1, modest improvement was observed from baseline in epidermal thickness and in numbers of CD3 and CD11c immune cells. At Week 12, statistically significant reductions in epidermal thickness and T-cell and inflammatory CD11c DC counts were observed for each guselkumab dose group compared with baseline ($p<0.05$ each). Langerhans cells, which are displaced in active psoriatic lesions, resumed a

normal panepidermal pattern in guselkumab-treated biopsy specimens at Week 12. No reduction was observed in epidermal thickness or T-cell density in placebo-treated subjects; however, a reduction from baseline in DC counts was observed for placebo at Week 12.

Affymetrix microarrays were used to define the transcriptome of lesional and nonlesional skin at baseline and weeks 1 and 12 after guselkumab treatment to assess the overall effect of guselkumab on the molecular disease profile. The disease profile was defined as 1224 transcripts (891 unique ENTREZ-annotated genes) with significant modulations in gene expression when comparing lesional with nonlesional biopsy specimens at baseline. These genes are highly characteristic of the psoriasis disease profile as previously reported. Of the 1224 disease-profile genes described, 1170 were normalized by 70% or greater in week-12 biopsy specimens of psoriatic lesions treated with high-dose (100 mg and 300 mg combined analyses) guselkumab.

Gene transcripts associated with epidermal hyperplasia, including keratin 6A (KRT6A) and Keratin 16 (KRT16) and STAT3, were decreased with guselkumab treatment to levels less than those observed in nonlesional skin, indicating a strong reduction in regenerative epidermal growth. Expressions of gene transcripts associated with the IL-23/Th17 pathway were also determined. Lipocalin 2 (LCN2), CXCL1, S100A7A (S100A15), S100A7 (psoriasin), S100A8, and S100A9, which are strongly induced by IL-17 in psoriatic lesions, were significantly decreased after guselkumab treatment. There was no impact on interferon gamma (IFNγ). These data suggest that IL-23 regulates expression of Th17 pathway gene targets in psoriasis lesions, with limited effect on Th1 pathway gene targets. Overall, the results demonstrated transcriptional changes consistent with the proposed mechanism of action of guselkumab and improvement in the psoriasis molecular disease profile.

Serum IL-17A levels were analyzed in PSO1001 at baseline and at Week 1 and Week 12 compared with placebo-treated subjects. Significant reductions from baseline in circulating IL 17A levels were observed at Week 1 ($p<0.05$) and Week 12 ($p<0.01$) in guselkumab responders, and no changes were observed in the placebo group. These data show that blockade of IL-23 with guselkumab reduces production of the effector cytokine IL-17A. Ten other serum proteins were analyzed for changes after treatment with guselkumab, including inflammatory proteins: IFN-γ, IL-1β, IL-6, TNF-α, IL-12p40, IL-12p70, IL-8, CRP, IL-23p19, and CCL22 (MDC). CCL22/MDC was the only analyte reduced at Week 12 after guselkumab treatment compared with placebo, which is aligned with the mechanism of action of guselkumab and the selective blockade of IL-23.

CNTO1959PSO2001 was a Phase 2, randomized, placebo- and active-comparator controlled, parallel group, multicenter, dose-ranging study of guselkumab in subjects with moderate to severe plaque psoriasis. The target population was men and women 18 years of age and older, with a diagnosis of plaque-type psoriasis with or without PsA for at least 6 months prior to first administration of study agent. Approximately 280 subjects were randomized equally to 1 of 7 groups (n = 40 per group). The placebo group received SC administration at Weeks 0, 4, and 8, followed by guselkumab 100 mg SC administration at Week 16 and q8w thereafter through Week 40. Guselkumab treatment groups received SC administration of 5 mg, 50 mg and 200 mg at Weeks 0, 4, 16 followed by q12w dosing thereafter through Week 40, or SC administration of 15 mg and 100 mg at Weeks 0, 4, 16 followed by q8w dosing thereafter through Week 40. The adalimumab treatment group received 80 mg SC administration at Week 0 followed by 40 mg SC administration at Week 1 and every other week thereafter through Week 39.

Serum levels of IL-17A, IL-17F, and IL-22, which are associated with the IL-23/Th17 pathway, were measured in Study PSO2001 as PD markers, in addition to a broad panel of 32 exploratory markers. As expected, based on the mechanism of action, significant reductions from baseline in serum IL 17A, IL 17F, and IL-22 levels were observed in guselkumab-treated subjects while no changes were observed

in the placebo group prior to cross over to guselkumab treatment. Guselkumab (100 mg) and adalimumab significantly reduced IL 17A and IL-17F serum levels compared to baseline and placebo at Week 4 and Week 16. Guselkumab achieved a significantly greater reduction of IL 17A and IL 17F compared to adalimumab at Week 28 and Week 52. Guselkumab achieved a rapid reduction of serum levels of IL-17A and IL-17F at Week 4 with a sustained effect for 12 weeks following last dose at Week 40.

Guselkumab also reduced serum IL-22 levels compared to adalimumab at Week 28 and Week 52 with a sustained effect for 12 weeks following the last dose at Week 40. Of the additional exploratory markers that were assessed, both guselkumab and adalimumab significantly reduced peripheral CCL22/MDC at Week 4 and Week 16 with a sustained effect for 12 weeks following the last dose at Week 40. Guselkumab and adalimumab showed a trend for reduction of S100A12 at Week 16 and Week 28, with a rebound observed following the last dose at Week 40. Adalimumab, but not guselkumab, impacted chemokine macrophage inflammatory protein-1β, while both guselkumab and adalimumab reduced peripheral interleukin 8 (CXCL8/IL-8); however, the effect with adalimumab on CXCL8/IL-8 was evident at Week 4 compared to a delayed effect of guselkumab observed at Week 28. No impact was observed on the other markers that were measured as part of the exploratory panel. In summary, blockade of IL-23 by guselkumab limited production of the effector cytokines 17A, IL-17F, and IL-22 which are associated with the IL-23/Th17 pathway. This suggests that inhibition of IL-23, a key regulatory cytokine that is required to some extent for the expansion of Th17, Th22, ILC3 and Tc17 cells, limits production of effector cytokines from IL-17 and IL-22 producing cells.

CNTO1959PSO3001 was a Phase 3, randomized, double-blind, multicenter, placebo- and active-comparator-controlled study of guselkumab in subjects with moderate to severe plaque-type psoriasis. The target population was adult men and women, with a diagnosis of plaque-type psoriasis (with or without psoriatic arthritis (PsA)) for at least 6 months before the first administration of study drug. Subjects must have had moderate to severe plaquetype psoriasis defined by the Investigator's Global Assessment (IGA) ≥ 3, Psoriasis Area and Severity Index (PASI) ≥ 12, and involved body surface area (BSA) ≥ 10%. Subjects must have been candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis.

In Study PSO3001, a subset of serum samples was analyzed for 6 analytes across a variety of protein classes including cytokines, chemokines and acute phase reactants as follows:

- Cytokines: IL-17A, IL-17F, IL-22, and IL-23
- Acute Phase Reactants: S100A12
- Chemokines: chemokine (C-X-C motif) ligand 1(CXCL)4, CXCL8

Analyses of a subset of these markers assessed the following objectives:

Evaluate the PD effects of treatment with guselkumab in a subset of subjects with moderate to severe plaque-type psoriasis at Weeks 4, 24, and 48, as compared to baseline.

Compare the PD effects of treatment with guselkumab versus adalimumab in a subset of subjects at Weeks 4, 24, and 48.

A subset of subjects (N=40 per arm) with similar demographic profiles was selected from Study PSO3001 for analysis of serum PD markers. Overall, the primary analyses of this subset of subjects from Study PSO3001 showed a demonstrable impact of guselkumab on disease - and mechanism-related biomarkers (eg, IL-17A, IL-17F and IL-22) that were maintained or further normalized following therapy in with guselkumab. IL-17A, IL-17F and IL-22 were significantly reduced at weeks 24

and week 48 (p≤ 0.001) compared to placebo. Guselkumab also reduced IL 17A (p≤ 0.05 at week 48), IL-17F (p≤ 0.05 at Weeks 4, 24 and 48) and IL-22 (p≤ 0.05 at Weeks 4 and 48) compared to adalimumab. These observations replicate findings from PSO 2001 with respect to the capacity of guselkumab to limit the production of effector cytokines IL 17A, IL-17F and IL-22 from IL-17 and IL-22 producing cells. These data also indicate that blockade of IL-23 in psoriasis has a greater impact on effector cytokines associated with the IL-23/Th17 axis compared to blockade of TNFα.

No secondary pharmacodynamics other than immunogenicity has been investigated.

The immunogenicity of guselkumab was analyzed using a sensitive and drug-tolerant ECLIA assay to detect antibodies to guselkumab. Additionally, all subjects positive for antibodies to guselkumab in Phase 2 and Phase 3 studies were assessed for the potential of these antibodies to neutralize the bioactivity of guselkumab (ie, NAbs to guselkumab) using a sensitive and drug tolerant competitive ligand binding assay.

A total of 1,730 subjects in Phase 2 and 3 psoriasis studies who received guselkumab had post treatment serum samples that were evaluable for antibodies to guselkumab. The overall incidence of antibodies to guselkumab though up to Week 52 after exposure to guselkumab was 5.5% (N=96). Titers of antibodies to guselkumab were generally low with the majority (76 of 96; 79.2%) being ≤ 1:160 up to 52 weeks after exposure to guselkumab.

An additional analysis was performed to determine the incidence of antibodies to guselkumab in subjects who received every scheduled guselkumab administration through Week 44 and had post treatment serum samples that were evaluable for antibodies to guselkumab. Among the 562 subjects in the PSO3001 and PSO3002 studies, the incidence of antibodies to guselkumab was 6.0%, which was consistent with the incidence of ADAs (5.5%) in the overall study population in the Phase 2 and 3 studies.

In the Phase 2 study (PSO2001), the development of antibodies to guselkumab did not appear to be associated with a reduction in the efficacy of guselkumab. Across guselkumab treatment groups, all (100%) of the 9 subjects who were positive for antibodies to guselkumab achieved a PASI 75 response at Week 40, while 167 (78.4%) of the 213 subjects who were negative for antibodies to guselkumab achieved a PASI 75 response at Week 40. Across guselkumab treatment groups, 5 (55.6%) of the 9 subjects who were positive for antibodies to guselkumab achieved a PGA score of cleared (0) or minimal (1) at Week 40, while 143 (67.1%) of the 213 subjects who were negative for antibodies to guselkumab achieved a PGA score of cleared (0) or minimal (1) at Week 40.

In the Phase 3 studies (PSO3001 and PSO3002), the development of antibodies to guselkumab and the titer of antibodies to guselkumab were not associated with a reduction in the clinical efficacy of guselkumab. This was evidenced by the finding that the proportions of subjects who achieved an IGA 0/1, IGA 0, PASI 90, or PASI 100 response at Week 44 (PSO3001) or Week 28 (PSO3002) were not impacted by the development of antibodies to guselkumab, or the titer levels of antibodies to guselkumab, through Week 44 (PSO3001) or Week 48 (PSO3002).

In the PSO3003 study, the development of antibodies to guselkumab was also not associated with a reduction in the clinical efficacy of guselkumab, as evidenced by the finding that the proportions of subjects who achieved an IGA 0/1 and at least 2-grade improvement (from Week 16) and a PASI 90 response at Week 36 were not impacted by the development of antibodies to guselkumab through Week 36.

All 96 subjects who were positive for antibodies to guselkumab from a total of 1,730 subjects in the Phase 2 and 3 studies in subjects with psoriasis (PSO2001, PSO3001, PSO3002, and PSO3003) were

evaluable for NAbs to guselkumab. Seven (7.3%) of 96 subjects were positive for NAbs. Therefore, the overall incidence of NAbs in subjects who received guselkumab and had samples that were evaluable for ADAs was 0.4% (7/1,730 subjects).

Psoriasis is strongly associated with certain human leucocyte-associated antigens, especially HLA-Cw*06:02. Patients who are HLA-Cw*06:02 positive have been reported to have more active disease and a younger age at disease onset than HLA-Cw6-negative patients (Gudjonsson JE, Karason A, Antonsdottir A, Runarsdottir EH, Hauksson VB, Upmanyu R, Gulcher J, Stefansson K, Valdimarsson H). Psoriasis patients who are homozygous for the HLA-Cw*0602 allele has a 2.5-fold increased risk of developing psoriasis compared with Cw6 heterozygotes (Br J Dermatol. 2003 Feb; 148(2):233-5.) The Applicant has analysed the disease onset characteristics and the therapeutic effects of the IL-12/IL-23 antagonist ustekinumab. It was confirmed the younger onset age of HLA-C*06:02-positive psoriasis patients. According to the published results the IL-12/IL-23 antagonist ustekinumab had somewhat better effect in the first 12 weeks of the treatment. Later the effects got rather even in both HLA-C*06:02-positive and negative patients. Data gained from the guselkumab treated patients are similar to those with ustekinumab.

Relationship between plasma concentration and effect

Dose- response study

In the Phase 2 PSO2001 study, the proportions of subjects who achieved a PGA score of cleared or minimal and PASI 75 responses were evaluated with respect to steady-state trough serum guselkumab concentration levels at Week 16 and 40. Overall, subjects who had trough serum guselkumab concentrations at the highest quartile level at Week 40 (>0.67 mcg/mL) had the highest response rates at Week 40. Moreover, only steady-state trough serum guselkumab concentrations at or above the highest quartile (0.67 mcg/mL) were associated with PASI and PGA rates for all response thresholds that substantially exceeded those reported for existing psoriasis therapies.

Phase 3 studies

Phase 3 Studies (PSO3001, PSO3002, and PSO3003)

In each individual Phase 3 study in subjects with psoriasis (PSO3001, PSO3002, and PSO3003), the proportions of subjects who achieved an IGA 0/1, IGA 0, PASI 90, and PASI 100 responses were evaluated with respect to steady-state trough serum guselkumab concentration levels to explore the observed relationship between systemic guselkumab exposure and clinical efficacy (improvement in IGA and PASI response rates). Based on the divergence of study designs after Week 28, data at Week 44 were selected for Study PSO3001, and the data at Week 28 were selected for PSO3002 because they represented the last steady-state trough serum guselkumab concentrations before the randomized withdrawal and retreatment phase.

With guselkumab 100 mg q8w SC administrations, consistently high efficacy responses were observed across all four steady-state trough serum guselkumab concentration quartile levels in both PSO3001 and PSO3002 studies This is expected since the majority (overall 72.5% in the PSO3001 and PSO3002 studies of subjects treated with the 100 mg q8w doses) achieved steady-state trough serum guselkumab concentrations >0.67 mcg/mL, a level which was associated with the highest clinical responses in Phase 2 study in subjects with psoriasis. Moreover, subjects with trough serum guselkumab concentrations below the highest quartile had slightly lower IGA responses, consistent with the fact that the 100 mg q8w dose regimen results in systemic guselkumab exposures that provide high efficacy near, but not at the plateau of the exposure-response curve. Similar findings

were observed for PASI 90 and PASI 100 response rates with respect to steady state trough serum guselkumab concentration levels.

2.4.4. Discussion on clinical pharmacology

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) 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 guselkumab have been extensively tested in a non-clinical pharmacology developmental program. The mechanism of action of guselkumab is the neutralization of human IL-23 thus inhibiting the IL-17 mediated immune response by the T helper 17 lymphocytes (Th17L).

The PK properties of guselkumab are similar to other human IgG1-type immunoglobulin-based mABs with few specific characteristics. It has linear pharmacokinetics and besides body weight no other extrinsic or intrinsic factor has a clinically significant effect on the kinetics. However, the bioavailability of the product compared to other IgG-based mABs is rather low, only 48.7%.

At PK level it was shown that guselkumab has a glycoform variant called M5 which had significantly shorter half-life than the other glycoforms. This fact suggested a receptor-mediated elimination pathway. However, it was agreed that this issue has little clinical relevance since M5 represented respectively less than 0.8% of the total amount of glycovariants and the kinetics of guselkumab is proven to be linear.

It is expected that the interaction potential of guselkumab is low. However, suppression inflammatory cytokines indirectly can enhance the drug metabolism rate. To address this issue, an additional Phase I interaction study (PSO1003) was submitted. This study was designed to evaluate the effect of a single SC dose of 200 mg guselkumab on the PK of a cocktail of representative probe substrates of CYP isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]). Based on the results of this study it can be concluded that the metabolic activities of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 are not affected by the decreased inflammation associated with the improvement of disease activity in subjects with psoriasis. These results are also in line with in vitro study using human hepatocytes which showed that IL-23 did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). The data has been appropriately reflected in section 4.5 of the SmPC.

Psoriasis is a common disorder and a number of locally applied medicines are available to treat it. Many of them are available without a prescription. Phototherapy (UV-A and UV-B) is another therapeutic modality used in practice. No information was provided on how guselkumab is distributed in the skin layers of the patients and how the intradermal distribution is related to the effect observed. In theory, the topically applied products could interfere with the action of guselkumab. Therefore, the Applicant was asked to discuss the possibility of interactions between guselkumab and concomitantly applied local therapeutic modalities. In its response, the Applicant acknowledged that no data are currently available on the efficacy or safety and tolerability of concurrent phototherapy or topical treatments in psoriasis patients being treated with guselkumab. In fact, the use of any additional active psoriasis systemic or topical treatments was prohibited during the first 48 weeks of studies PSO3001 and PSO3002 which is consistent with nearly all other randomized clinical trials of biologic agents in psoriasis performed to date.

There are, however, published results from several clinical trials that have investigated the addition of topical psoriasis therapies to biologics with the intent of maintaining initial responses. The currently available data, though limited, suggest that using topical therapies as an adjunct treatment to biologics

is a well-tolerated and effective means of controlling psoriasis and improving the quality of life for patients. A recent publication that reviewed the available published data on combining biologic and phototherapy treatments for moderate-to- severe psoriasis concluded that 9 out of 10 of the published studies included, demonstrated favourable efficacy and safety for combining biologic and phototherapy. Based on the response it has been concluded that additional explicit warning regarding concomitant local therapy is not needed.

At the SmPC recommended posology, the steady-state plasma levels will be in the range where the maximum therapeutic effect is expected. However, from the literature, it was known that obesity itself is a contributing pathological factor. Therefore additional analysis was suggested to check the benefit of dose adjustment for obese patients using BMI instead of BWT as an indicator for obesity. The additional POP-PK/PD analysis and simulations demonstrated that BMI and BWT are equally good predictors, and a specific obesity-related effect could not be demonstrated. Therefore BMI-based dosing is not warranted.

Biomarker data was collected from a phase 1, a phase 2 and the phase 3 PSO3001 studies.

The biomarker analyses have adequately proven the mechanism of action of guselkumab in humans. The changes of serum levels of IL-17A, IL-17F and IL-22 were decreased by time and levelled around week 24 parallel with the improvement of psoriasis symptoms (please, refer to efficacy analyses).

Overall, the findings from the histological analyses are consistent with the mechanism of action of guselkumab and with the clinical efficacy observed.

No secondary pharmacodynamics other than immunogenicity has been addressed by the Applicant. Since guselkumab shows high specificity to IL-23 proven by the non-clinical pharmacology studies, and non-clinical safety and toxicology studies have not revealed any unexpected effects, secondary pharmacodynamics (off-target related effects) are not expected. The Fc fragment of guselkumab is not involved in the mechanism of action and no complement activation has been observed either. The immunogenicity of guselkumab was analysed using a sensitive and drug-tolerant ECLIA assay to detect antibodies to guselkumab. Additionally, all subjects positive for antibodies to guselkumab in Phase 2 and Phase 3 studies were assessed for the potential of these antibodies to neutralize the bioactivity of guselkumab (ie, NAbs to guselkumab) using a sensitive and drug tolerant competitive ligand binding assay. The overall incidence of antibodies against guselkumab was low (96 subjects of 1730, 5.5%). Of this 96 of subjects 7 were positive for neutralizing antibodies. Efficacy was not influenced by the antibodies. For detailed analysis, please, refer to the efficacy and safety sections of the report.

There were no clinical studies designed and conducted to evaluate pharmacodynamic interactions with other medicinal products. Since guselkumab is a highly specific monoclonal antibody against IL-23 and it has no other efficacy targets, pharmacodynamic interactions are not anticipated. The lack of interaction data is reflected in the SmPC (please see SmPC section 4.5).

Psoriasis is strongly associated with certain human leucocyte-associated antigens, especially HLA-Cw*06:02. Patients who are HLA-Cw*06:02 positive have been reported to have more active disease and a younger age at disease onset than HLA-Cw6-negative patients (Gudjonsson JE, Karason A, Antonsdottir A, Runarsdottir EH, Hauksson VB, Upmanyu R, Gulcher J, Stefansson K, Valdimarsson H). Psoriasis patients who are homozygous for the HLA-Cw*0602 allele have a 2.5-fold increased risk of developing psoriasis compared with Cw6 heterozygotes. (Br J Dermatol. 2003 Feb; 148(2):233-5). The Applicant has analysed the disease onset characteristics and the therapeutic effects of the IL-12/IL-23 antagonist ustekinumab and the specific IL-23 antagonist guselkumab, confirming the younger onset age of HLA-C*06:02-positive psoriasis patients. Guselkumab was at least as effective in HLA-Cw*06:02 positive patients as in the HLA-Cw*06:02 negative ones.

From a pharmacodynamics point of view it is worth noting that the mechanism of action of guselkumab is most likely the same in the HLA-C*06:02-positive subjects as in the HLA-C*06:02-negative ones. Due to the small sample size firm conclusion cannot be drawn whether guselkumab may even be more efficient in HLA-C* 06:02-positive subjects. Nevertheless the data indicate that the therapeutic effect of guselkumab is present and at least as pronounced as in the HLA-C*06:02-negative subjects.

This genetic difference might even improve but definitely does not impair the effect of guselkumab although further data would be necessary to fully evaluate the impact of the genetic difference on the therapeutic effect of guselkumab.

2.4.5. Conclusions on clinical pharmacology

A firm relationship has been demonstrated between dose, plasma concentration and the therapeutic effect. Biomarkers have been evaluated in three clinical studies. Guselkumab efficiently reduced the biomarkers related to psoriasis and showed more efficiency than the TNFα antagonist adalimumab. The proof of concept has been justified. The clinical pharmacology data submitted in support of this marketing authorisation is considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study PSO1001 (phase 1, proof-of-concept) demonstrated proof of concept of guselkumab efficacy in psoriasis subjects at all guselkumab dose levels examined (10 mg, 30 mg, 100 mg, and 300 mg single doses), and all doses were well tolerated. PK analysis showed that guselkumab exhibited approximately dose proportional PK across the dose range tested with a mean half-life of approximately 17 days. Based on preliminary exposure-response modeling and simulation, a Phase 2 dose ranging study (PSO2001) including five dose levels (5, 15, 50, 100, and 200 mg) and two dosing intervals (q8w and q12w) was conducted to further characterize the guselkumab dose- and exposure-response in psoriasis.

Study PSO2001 (phase 2, "X-PLORE")

The Phase 2 study PSO2001 was a randomized, placebo- and active-comparator-controlled, multicenter dose-ranging study of guselkumab in subjects with moderate to severe plaque psoriasis. A total of 293 subjects were randomized in the study.

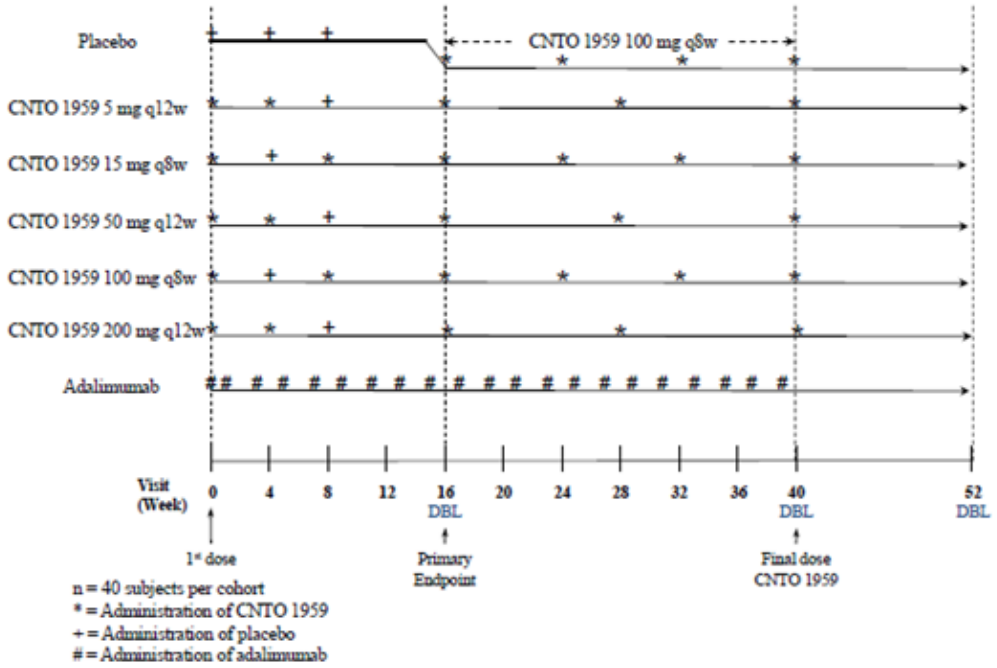
Two dose regimens were evaluated in this study:

q8w dosing for the 15 and 100 mg arms (Weeks 0, 8, and q8w thereafter through Week 40) and

q12w dosing after induction doses for the 5, 50, and 200 mg arms (Weeks 0, 4, 16, and q12w thereafter through Week 40).

Subjects were to be randomly allocated in equal proportions to 1 of 7 groups to receive: placebo, 5 dose groups for guselkumab (5 mg at Weeks 0 and 4 then every 12 weeks [q12w] through Week 40, 15 mg every 8 weeks [q8w], 50 mg at Week 0 and Week 4 then q12w, 100 mg q8w, and 200 mg at Weeks 0 and 4 then q12w), or open-label adalimumab (80 mg SC at Week 0 followed by 40 mg SC administration at Week 1 and every other week through Week 39).

Figure 2 - Schematic Overview of Study PSO2001



The results of study PSO2001 showed efficacy in all guselkumab doses studied. A significantly greater proportion of subjects in each guselkumab dose group achieved a PGA of cleared (0) or minimal (1) (all $p \leq 0.002$) and PASI 75 (all $p < 0.001$) at Week 16 than in the placebo group. Also, a substantially greater proportion of subjects in the guselkumab 50 mg q12w, 100 mg q8w, and 200 mg q12w groups achieved PGA 0/1 than in the adalimumab group at Week 16. When comparing q8w versus q12w dose regimens, a loss of efficacy toward the end of each dosing interval was evident for the q12w dosing groups that were not apparent among subjects receiving q8w dosing. Therefore, it was concluded that a q8w dosing interval would provide a more sustained efficacy than a q12w dosing interval.

A clear dose-response in efficacy was observed across several clinically important PASI and IGA measures of response from the 5 mg dose regimen up to the 100 mg dose regimen. The dose response was most apparent at the higher PASI and PGA thresholds (eg, PASI 90 and 100 responses, and PGA 0). For example, PASI 100 response rates of 9.8%, 12.2%, 19.0%, 33.3% and 28.6 % at Week 16 were observed in subjects treated with 5 mg, 15 mg, 50 mg, 100 mg and 200 mg dosing regimens, respectively. The study results therefore showed that the 100 mg q8w dose regimen had the best efficacy among all dose regimens studied. Dose regimens lower than 100 mg q8w were consistently less effective and the dose regimen of 200 mg q12w did not provide incremental benefit over 100 mg q8w.

Figure 3 - Percent of Subjects Achieving PGA Score of Cleared (0) or Minimal (1) Through Week 52 by Visit; Randomized Subjects

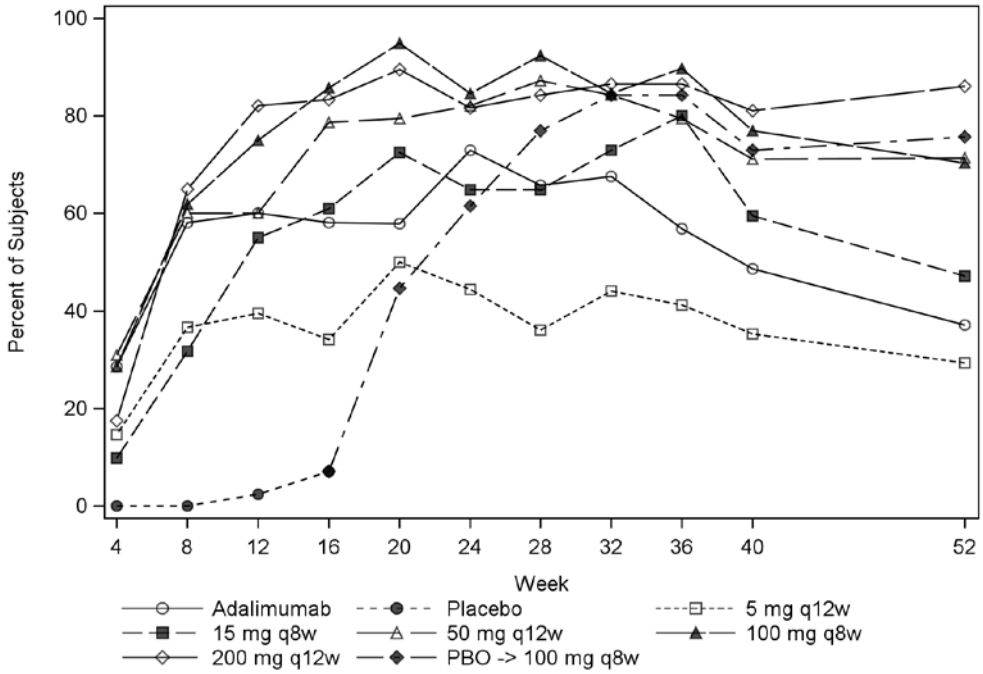
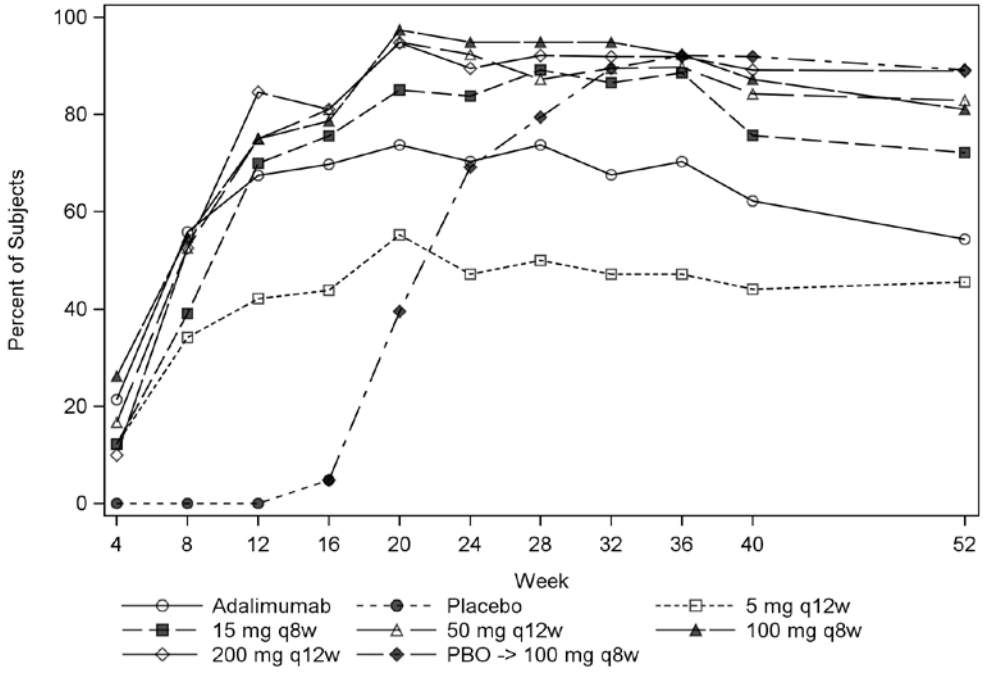


Figure 4 - Percent of Subjects Achieving PASI 75 Response Through Week 52 by Visit; Randomized Subjects



At Week 16, all guselkumab groups had significantly greater improvements (ie, decreases) in DLQI scores compared with the placebo group. In addition, a significantly greater proportion of subjects in all guselkumab groups achieved a DLQI score of 0 or 1, indicating that was little or no effect of psoriasis on subjects health related quality of life, at Week 16 compared with the placebo group. Subjects in a higher dose group were more likely to achieve a DLQI score of 0 or 1 at Week 16 than

those in lower dose groups, indicating a dose-response relationship. DLQI score improvements achieved at Week 16 were sustained through Week 28 and Week 52 in all guselkumab groups, and the improvements were generally comparable with the adalimumab group.

A clear exposure-response relationship was also evident in analyses based on clinical response by trough serum guselkumab concentrations in study PSO2001 (see PK section).

Based on the clear dose- and exposure response relationships defined in Phase 2, and a goal of maintaining trough serum guselkumab concentrations $\geq$ 0.67 μg/mL in the majority of subjects so that the highest efficacy level could be achieved, the 100 mg q8w dose regimen was selected for study in Phase 3. To expedite the onset of response, a loading dose of 100 mg guselkumab was also given at Week 4 prior to 100 mg q8w maintenance dosing in the Phase 3 program.

2.5.2. Main studies

A global Phase 3 program consisting of 3 studies (PSO3001, PSO3002, and PSO3003) is ongoing to investigate the efficacy and safety of SC guselkumab in subjects with moderate to severe plaque psoriasis. Guselkumab treatment was compared with adalimumab treatment in both PSO3001 and PSO3002. Study PSO3003 examined the efficacy of guselkumab in subjects with an inadequate response to ustekinumab. The longer-term efficacy and safety of guselkumab is being assessed in 4-year extensions of studies PSO3001 and PSO3002 (ie, both studies will have an overall study duration of 5 years).

The Phase 3 clinical development program for guselkumab included 2,700 adult subjects (837 in PSO3001, 992 in PSO3002, and 871 in PSO3003) with moderate to severe plaque psoriasis, encountered in clinical practice, who were candidates for phototherapy or systemic therapy.

Methods

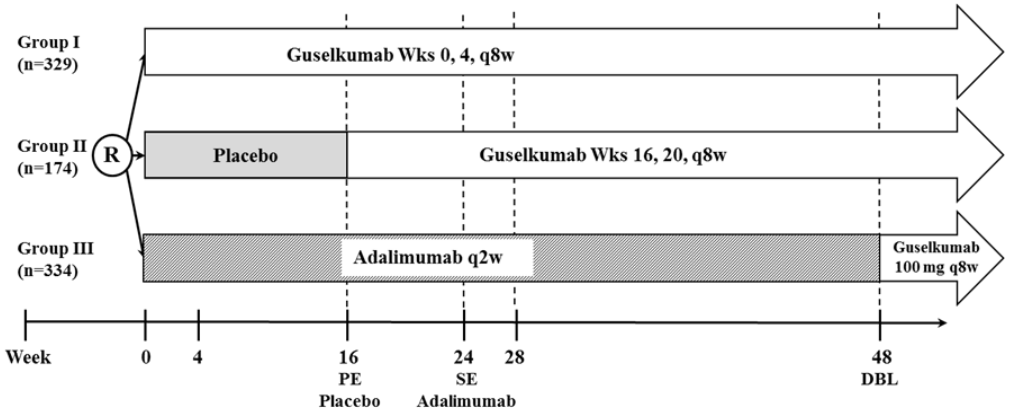
Study Participants

The target population for the guselkumab global Phase 3 clinical program was adults with moderate to severe plaque-type psoriasis (with or without PsA) for at least 6 months prior to first administration of study agent. Moderate to severe plaque type psoriasis was defined as an IGA ≥3, PASI ≥12, and BSA ≥10%. Subjects must have been candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis. Subjects with nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) were excluded. Following patients were also excluded: those who had concurrent active infection or history or latent or active granulomatous infection (including TB), nontuberculous mycobacterial infection, serious opportunistic infection, chronic or recurrent infectious disease, or infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C, history of malignancy or those who underwent organ transplantation or had serious zoster infection.Subjects who had ever received guselkumab were excluded from all Phase 3 studies, while subjects who had ever received adalimumab were excluded from studies PSO3001 and PSO3002, and subjects who had ever received ustekinumab were excluded from study PSO3003.

Treatments

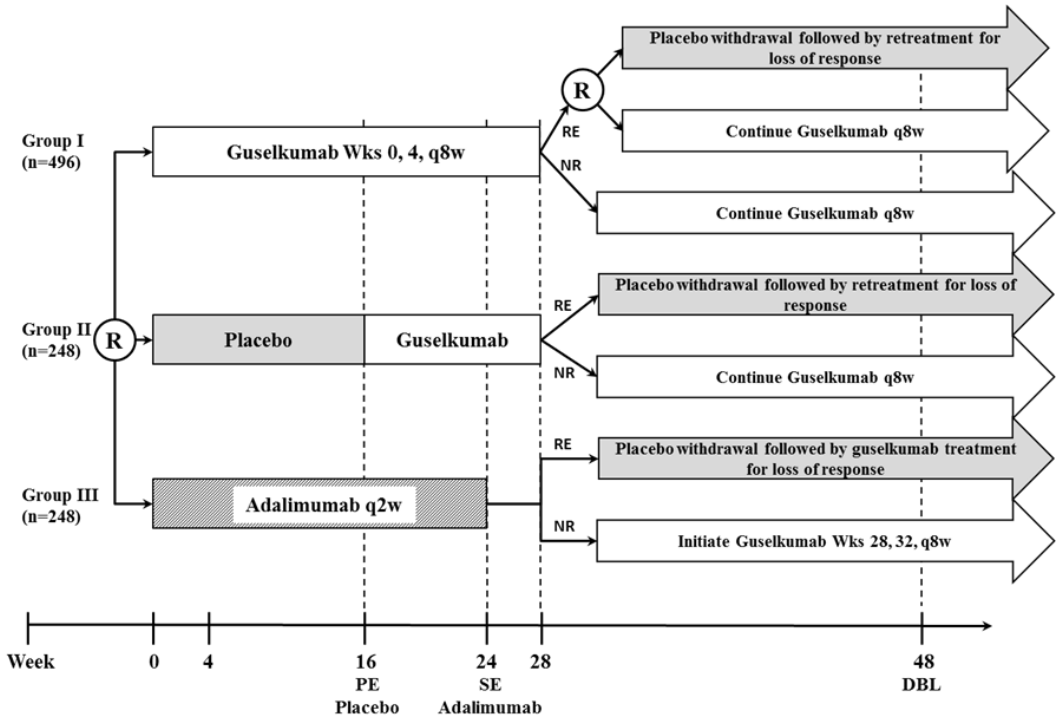
Global studies PSO3001 and PSO3002 are placebo- and active-comparator controlled studies with identical study designs through Week 24, to assess the efficacy, safety, pharmacokinetics, and immunogenicity of guselkumab in subjects with moderate to severe plaque psoriasis who are candidate for phototherapy or systemic therapy (Figure 5 and Figure 6).

Figure 5 - Schematic Overview of Study CNTO1959PSO3001



DBL = database lock; PE = primary endpoint; R = randomization; SE = secondary endpoint

Figure 6 - Schematic Overview of Study CNTO1959PSO3002



DBL = database lock; NR = nonresponder (<PASI 90); PE = primary endpoint; R = randomization; RE= responder (≥ PASI 90); SE = secondary endpoint

The designs then diverge beyond Week 24, with each study addressing a distinct aspect of psoriasis treatment between Weeks 24 and 48. In the PSO3001 study, treatment of subjects randomized to guselkumab and adalimumab continued through Week 48 to allow for a robust evaluation of the durability of response and comparative efficacy and safety during one year of continuous treatment. Study PSO3002 incorporated randomized withdrawal and retreatment design elements from Week 28 and beyond, to formally assess the efficacy and safety of guselkumab maintenance dosing relative to withdrawal of treatment in PASI 90 responders.

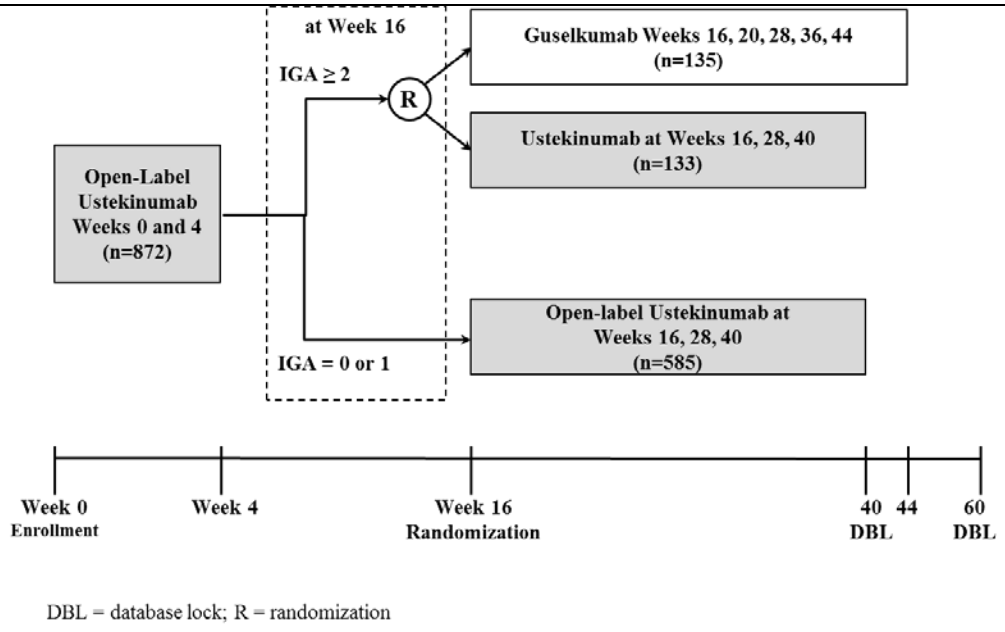
Study PSO3002 also provides efficacy and safety information on adalimumab PASI 90 nonresponders who transitioned to guselkumab treatment at Week 28. A total of 837 subjects were randomized to the placebo (n=174), guselkumab (n=329) or adalimumab (n=334) groups in study PSO3001 and a total of 992 subjects were randomized to the placebo (n=248), guselkumab (n=496), and adalimumab (n=248) in study PSO3002. Results for both studies reported in this submission reflect data available through the Week 48 database lock.

Self-administration of study drug was incorporated in the PSO3001 and PSO3002 studies. Subjects were trained to self-administer study drug at the study site at Week 0 using the liquid formulation in prefilled syringe (PFS) assembled with a passive needle guard (PFS-U), which is to be the marketed presentation of guselkumab. After appropriate training, subjects self-administered study drug at home through Week 47 in PSO3001 and through Week 23 in PSO3002. Starting at Week 28 in study PSO3002, subjects self-administered study drug at the study site due to the less frequent dosing during the randomized withdrawal and retreatment phase of the study. The following doses were applied: guselkumab 100 mg at weeks 0, 4, and 12 and every 8 weeks thereafter, placebo beginning at Week 0 followed by guselkumab 100 mg at Week 16 and Week 20 , adalimumab (80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks thereafter (q2w) and ustekinumab dose of 45 mg or 90 mg (according to the subject's baseline [week 0] weight) at Weeks 0 and 4. At Week 16 and every 12 weeks (q12w).

The third global Phase 3 study (PSO3003) used an enrichment study design to assess the benefit of guselkumab treatment in subjects who demonstrated an inadequate response (IGA≥2) to ustekinumab after 16 weeks of treatment. The target population enrolled at Week 0 for PSO3003 shared similar key eligibility criteria to that defined for studies PSO3001 and PSO3002, ie subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and similar exclusion criteria were applied. A total of 871 subjects were enrolled and received open-label ustekinumab. At Week 16, subjects with an IGA ≥2 were randomized in a 1:1 ratio to either initiate guselkumab 100 mg at Weeks 16 and 20, and q8w thereafter or continue on ustekinumab q12w. Visits were every 4 weeks (q4w) through Week 44 for efficacy and safety evaluations, with an additional follow-up visit at Week 52 and a final safety visit at Week 60. The objective of study was intended to provide guidance for clinicians for those patients that have not achieved a satisfactory psoriasis response prior to administration of ustekinumab. Data for study PSO3003 reported in this submission reflect data available through the Week 40 database lock.

Figure 7 - Schematic Overview of study CNTO1959PSO3003

Figure 7 - Schematic Overview of study CNTO1959PSO3003



DBL = database lock; R = randomization

Objectives

Studies CNTO1959PSO3001 and CNTO1959PSO3002 (VOYAGE I and II)

Primary: efficacy, safety and tolerability of guselkumab

Secondary: To compare the efficacy of guselkumab to adalimumab

Maintenance of response (only in study 3002)

To evaluate the effect of treatment with guselkumab on other measures of signs and symptoms of psoriasis

Health-related quality of life

Other secondary: PK, immunogenicity

Exploratory: pharmacodynamics endpoints (biomarkers)

Association of efficacy (1) or psoriasis (2) and genetic/epigenetic factors

Study CNTO1959PSO3003 (NAVIGATE)

Primary: To compare the efficacy of the following 2 treatment paradigms in subjects who have achieved an inadequate (Investigator's Global Assessment [IGA]≥2) response to ustekinumab at Week 16:

1) switching to guselkumab treatment, or

2) remaining on ustekinumab treatment, and to assess the safety and tolerability of guselkumab in subjects with moderate to severe plaque-type psoriasis and an inadequate (IGA≥2) response to ustekinumab at Week 16.

Secondary: To evaluate the effect of switching to guselkumab on patient-reported signs and symptoms of psoriasis for subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16, and to assess the pharmacokinetics (PK) and immunogenicity of guselkumab after subcutaneous (SC) administrations in subjects with moderate to severe plaque-type psoriasis and an inadequate (IGA≥2) response to ustekinumab at Week 16.

Exploratory: To assess the pharmacodynamics of treatment (biomarkers) in subjects with moderate to severe plaque-type psoriasis and an inadequate (IGA≥2) response to ustekinumab at Week 16 and aid in evaluating the drug-clinical response relationship, and to explore the association between genetic and epigenetic factors, and 1) the efficacy of guselkumab or ustekinumab and 2) psoriasis.

Outcomes/endpoints

Endpoints

Key measures used to evaluate efficacy of guselkumab in both studies PSO3001 and PSO3002 included:

- Psoriasis improvement measures: Psoriasis Area and Severity Index **(PASI)** and Investigator's Global Assessment **(IGA).** Notably, the Sponsor modified the 6-point PGA by collapsing the 2 highest categories (marked [4] and severe [5]) into 1 (severe [4]). This modified 5-point static global assessment was used in the guselkumab Phase 3 program, and is referred to as the Investigator Global Assessment (IGA) to distinguish it from the 6-point PGA used previously in study PSO2001.

- Regional psoriasis measures: Scalp Specific Investigator Global Assessment **(ss-IGA),** Physician's Global Assessment of Hands and/or Feet **(hf-PGA),** Nail Psoriasis Severity Index **(NAPSI),** and fingernail PGA **(f-PGA)**

- Patient-reported outcomes measures (PRO):

  Dermatology Life Quality of Index **(DLQI)**

  Psoriasis Symptom and Sign Diary (**PSSD).** It is a PRO instrument that has been designed and validated by the Sponsor to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit.

Additional patient-reported outcome efficacy measures only used in **study PSO3002** included the 36-item Short Form Health Survey **(SF-36),** Hospital Anxiety and Depression Scale **(HADS),** and Work Limitations Questionnaire **(WLQ).**

The primary and major secondary endpoints evaluated for the Phase 3 psoriasis studies are presented by order of testing in table 14 and table 15. Multiplicity was controlled using fixed sequence testing for both the primary and major secondary endpoints in all studies. Studies PSO3001 and PSO3002 shared the same co-primary endpoints and major secondary endpoints through Week 24. The endpoints at Week 48 focused on guselkumab comparisons with adalimumab in PSO3001 and a randomized assessment of efficacy of maintenance of therapy compared with withdrawal in PSO3002. Endpoints in study PSO3003 were from Week 28 through Week 40 and focused on comparisons of guselkumab to ustekinumab in subjects who were ustekinumab inadequate responders (IGA≥2) at Week 16 and randomized to guselkumab or ustekinumab at Week 16.

Table 14 - Efficacy Endpoints for Phase 3 Clinical Studies PSO3001 and PSO3002

	Guselkumab vs Placebo	Guselkumab vs Adalimumab	Maintenance vs Withdrawal
Co-primary endpoints [a]			
Proportion of subjects who achieved IGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16	3001/3002		
Major secondary endpoints [a]			
Proportion of subjects who achieved IGA 0 at Week 24 [b]		3001/3002	
Proportion of subjects who achieved IGA 0/1 at Week 24 [b]		3001/3002	
Proportion of subjects who achieved PASI 90 response at Week 24 [b]		3001/3002	
The time to loss of PASI 90 response at Week 28 to Week 48			3002
Proportion of subjects who achieved an IGA 0 at Week 48 [b]		3001	
Proportion of subjects who achieved an IGA 0/1 at Week 48[b]		3001	
Proportion of subjects who achieved PASI 90 response at Week 48[b]		3001	
Change from baseline in DLQI score at Week 16	3001/3002		
Proportion of subjects who achieved an IGA 0/1 at Week 16[c]		3001/3002	
Proportion of subjects who achieved PASI 90 response at Week 16[c]		3001/3002	
Proportion of subjects who achieved PASI 75 response at Week 16[c]		3001/3002	
Proportion of subjects who achieved ss-IGA 0/1 at Week 16[d]	3001/3002		
Change from baseline in PSSD symptom score at Week 16	3001/3002		
Proportion of subjects with PSSD symptom score=0 at Week 24[b]		3001/3002	

[a] To control the overall Type 1 error rate (p=0.05), the primary analysis and major secondary analyses were tested using a fixed sequence method. Specifically, the first major secondary endpoint was tested only if the co-primary endpoints were positive, and subsequent endpoints were tested only if the preceding endpoint in the sequence was positive.
[b] Tested for superiority of the guselkumab group compared with the adalimumab group.
[c] Tested for noninferiority of the guselkumab group compared with the adalimumab group for the three endpoints in the above order before any of the superiority tests for the same endpoints in the above order.
[d] Included only randomized subjects with baseline ss-IGA score ≥2.
DLQI=Dermatology Life Quality Index, IGA 0= IGA (Investigator's Global Assessment) response of cleared (0), IGA 0/=IGA response of cleared (0) or minimal (1), PASI=Psoriasis Area and Severity Index , PASI 75=≥75% improvement in PASI score from baseline, PASI 90=≥90% improvement in PASI score from baseline, PSSD=Psoriasis Symptom and Sign Diary, and ss-IGA=Scalp Specific Investigator Global Assessment

Table 15 - Efficacy Endpoints for the Phase 3 Clinical Study PSO3003

Primary endpoint[a]	
Number of visits[b] at which subjects achieved IGA 0/1 and ≥2-grade improvement (relative to Week 16)	from Week 28 through Week 40
Major secondary endpoints[a]	
Number of visits[b] at which subjects achieved PASI 90 between Week 28 and Week 40	
Number of visits[b] at which subjects achieved IGA 0 between Week 28 and Week 40	
Proportion of subjects with IGA 0/1 and ≥ 2-grade improvement (relative to Week 16) at Week 28	

[a] Comparisons are for guselkumab versus ustekinumab
[b] Maximum number of visits from Week 28 through Week 40 = 4.
IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index;

Since studies PSO3001 and PSO3002 were large and each provided a robust estimate of guselkumab efficacy, these two studies were not pooled for estimating efficacy rates. Instead, the results of each of these studies are presented side by side to allow for an assessment of consistency. However, efficacy data were pooled from PSO3001 and PSO3002 to evaluate efficacy in subpopulations, efficacy by serum guselkumab concentration at trough level, and efficacy by antibody to guselkumab status to increase the sample size and precision for these evaluations.

Sample size

Study CNTO1959PSO3001

The assumptions for the sample size and power calculations were based on the data from the guselkumab CNTO1959PSO2001 study.

Based on the assumptions (more detail in the protocol), with a total of approximately 750 subjects to be randomized in a 2:1:2 ratio to guselkumab 100 mg q8w (n=300), placebo (n=150), and adalimumab (n=300) at Week 0:

- There was >99% power to detect significant differences for both co-primary endpoints in the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieved a PASI 90 response between the placebo and guselkumab groups at Week 16, at a significance level of 0.05.
- There was >99% power to detect significant differences in the proportion of subjects achieving an IGA score of cleared (0) between the adalimumab and guselkumab groups at Week 24 or Week 48 at a significance level of 0.05.
- There was at least 97% power to detect significant differences in the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) between the adalimumab and guselkumab groups at Week 24 or Week 48 at a significance level of 0.05.

There was at least 90% power to detect a 12 percentage-point difference in the proportion of subjects achieving a PASI 75 response between the adalimumab and guselkumab groups at Week 16 at a significance level of 0.05.

Study CNTO1959PSO3002

The assumptions for the sample size and power calculations were based on the data from the guselkumab CNTO1959PSO2001 study.

Based on the above assumptions, with a total of approximately 1,000 subjects to be randomized in a 2:1:1 ratio to guselkumab 100 mg q8w (n=500), placebo (n=250), and adalimumab (n=250) at Week 0:

- There was >99% power to detect significant differences for both co-primary endpoints in the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) and the proportion of subjects achieving a PASI 90 response between the placebo and guselkumab groups at Week 16, at a significance level of 0.05.

- There was at least 98% power to detect significant differences in the proportion of subjects achieving an IGA score of cleared (0) and IGA score of cleared (0) or minimal (1) between the adalimumab and guselkumab groups at Week 24 at a significance level of 0.05.

- The assumption was made that approximately 70% of the subjects originally randomized to guselkumab were to be PASI 90 responders (based on the CNTO1959PSO2001 data) and were randomized in a 1:1 ratio to either receive guselkumab 100 mg q8w or undergo withdrawal of guselkumab at Week 28. This ensured at least 90% power to detect a 15-percentage-point difference in PASI 90 response rates at Week 48 between these 2 groups at a significance level of 0.05.

In addition, there was at least 90% power to detect a 12-percentage-point difference in the proportion of subjects achieving a PASI 75 response between the adalimumab and guselkumab groups at Week 16 at a significance level of 0.05.

Study CNTO1959PSO3003

The sample size was chosen to achieve at least 90% power to detect treatment differences between ustekinumab and guselkumab for the primary and major secondary endpoints at a significance level of 0.05 (2-sided).

For subjects who continued on ustekinumab treatment, the assumptions for sample size and power calculations were based on data from the ustekinumab Phase 3 psoriasis studies (C0743T08 and C0743T09).

For subjects who switched from ustekinumab to guselkumab, the assumptions for sample size and power calculations were derived by comparing the ustekinumab response rates in the ustekinumab Phase 3 psoriasis studies (C0743T08 and C0743T09) with those from the guselkumab X-PLORE study

With approximately 800 subjects receiving open-label ustekinumab (45 mg for those with baseline [Week 0] weight ≤100 kg and 90 mg for those with baseline [Week 0] weight >100 kg) at Week 0, assuming 5% of the subjects discontinued study drug before Week 16, it was expected that approximately 260 subjects would achieve an IGA≥2 and be randomized in a 1:1 ratio at Week 16 to either switch to guselkumab 100 mg at Weeks 16 and 20 and then q8w thereafter, or continue in the ustekinumab treatment group.

Based on the efficacy assumptions at various time point (weeks 16-40)130 subjects per treatment group would have approximately 98% power to detect the treatment difference at a significance level of 0.05.

Sufficient power (>90%) could also be achieved assuming a smaller treatment effect.

Randomisation

Studies CNTO1959PSO3001 and CNTO1959PSO3002 (VOYAGE I and II)

At Week 0, subjects were randomly assigned to 1 of 3 treatment groups (guselkumab 100 mg, placebo, and adalimumab) in a 2:1:2 ratio in study 3001, and randomly assigned to 1 of 3 treatment groups in study 3002 based on a computer-generated randomization schedule). Permuted block randomization *with stratification by investigator site* was used.

In study 3002, at Week 28, subjects randomized to guselkumab 100 mg q8w who were PASI 90 responders were rerandomized using the IWRS either to placebo or guselkumab 100 mg q8w in a 1:1 ratio.

Study CNTO1959PSO3003 (NAVIGATE)

Approximately 260 subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16 were planned to be randomly assigned to 1 of 2 treatment groups (guselkumab [n=130], ustekinumab [n=130]) in a 1:1 ratio. The randomization was based on a dynamic randomization method, *stratified by site and baseline (Week 0) weight (≤100 kg, >100 kg)* with a biased coin assignment.

Blinding (masking)

Studies CNTO1959PSO3001 and CNTO1959PSO3002 (VOYAGE I and II)

Studies were double blinded until week 48.

To maintain blind, subjects received 2 types of syringes. Subjects randomized to guselkumab received guselkumab (and placebo for guselkumab at Week 16 only) in PFS-U and placebo for adalimumab. Subjects randomized to placebo received: placebo for guselkumab in PFS-U and placebo for adalimumab. Subjects randomized to adalimumab received adalimumab and placebo for guselkumab.

Study CNTO1959PSO3003 (NAVIGATE)

Open-label ustekinumab treatment period was followed by a double blind phase.

Statistical methods

For studies PSO3001 and PSO3002, the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by investigator site was used to compare the proportion of subjects responding to treatment. For study PSO3003, CMH mean scores test stratified by baseline (Week 0) weight (≤100 kg, >100 kg) was used to compare the number of visits during which a clinical response was observed from Week 28 through Week 40. Continuous response parameters were compared using an analysis of variance model or rank-based analysis of variance with investigator site as a covariate (PSO3001 and PSO3002) or with baseline (Week 0) weight (PSO3003) as a covariate. Log-rank test stratified by investigator site was used to compare the time to event endpoint in PSO3002. All statistical testing for superiority was performed 2-sided at a significance level of 0.05 and for non-inferiority 1-sided at a significance level of 0.025 for both studies PSO3001 and PSO3002.

To control the overall Type 1 error rate of 0.05, the primary analysis and major secondary analyses were tested in a fixed sequence in the order shown in Table 14 (PSO3001 and PSO3002) and Table 15 (PSO3003). That is, the first major secondary endpoint was tested only if the primary endpoint(s) was positive, and the subsequent endpoint was tested only if the preceding major secondary endpoint in the sequence was positive. Nominal p-values were reported for all other secondary analyses.

Subjects who discontinued the study agent due to lack of efficacy or an adverse event of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis were considered treatment failures. The baseline values were assigned regardless of the observed data for continuous endpoints, zero was assigned to improvement and percent improvement, and non-responder status was assigned to binary response variables. After applying the treatment failure rules, remaining missing data were in general handled as follows:

- Nonresponder imputation was applied for binary endpoints.
- Last observation carried forward was applied for continuous variables.

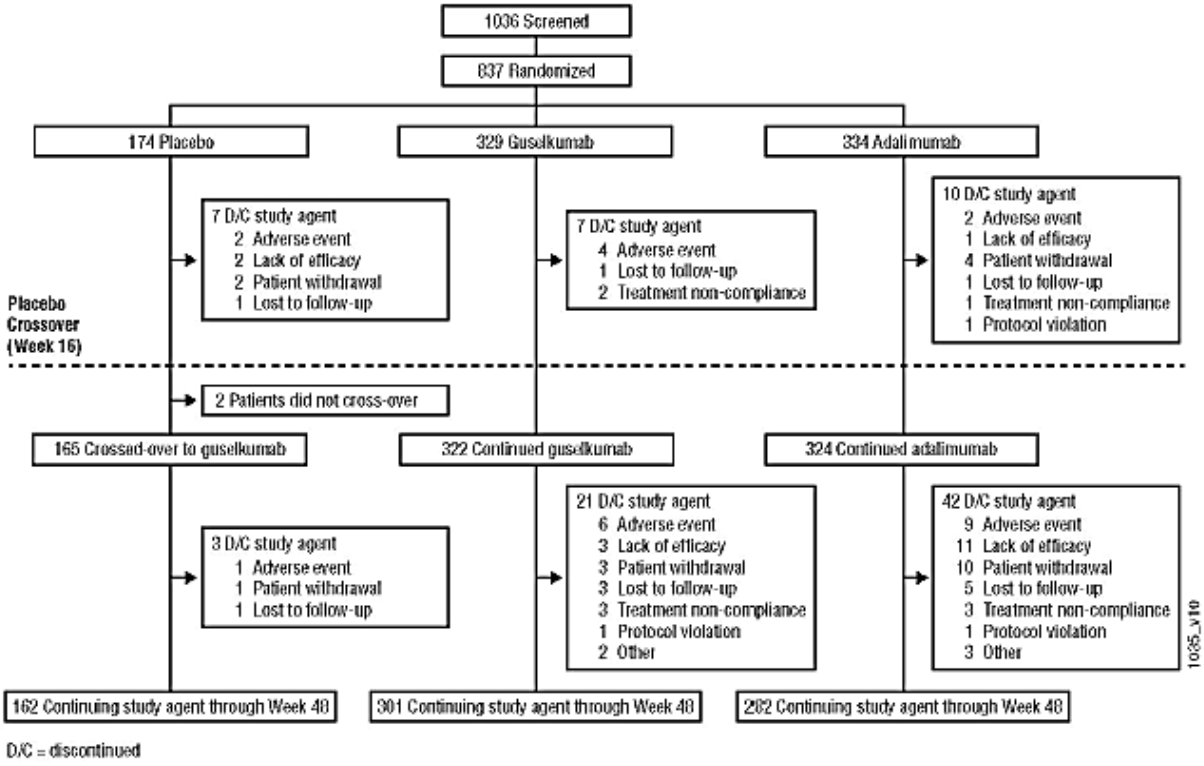
Additionally, the randomization method for study PSO3003 was performed using dynamic randomization with a bias coin assignment to accommodate the stratification by both weight and investigator site. A sensitivity analysis using a re-randomization test for the primary endpoint was performed.

Results

Participant flow

Study CNTO1959PSO3001

Figure 8 - Subject Disposition in Study CNTO1959PSO3001



Source:

[TSIDS01A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDS01A.SAS] 29MAY2016, 05:59;
[TSIDS01B.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDS01B.SAS] 29MAY2016, 05:59;
[TSITG02A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSITG02A.SAS] 29MAY2016, 05:59;
[TSITG01B.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSITG01B.SAS] 29MAY2016, 05:59;
[LSIDS01.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\LSIDS01.SAS] 28JUN2016, 14:58.

Table 16 - Number of Subjects Who Discontinued Study Agent Through Week 16; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0	174	329	334	837
Subjects treated with study agent	174 (100.0%)	329 (100.0%)	333 (99.7%)	836 (99.9%)
Subjects who discontinued study agent[a]	7 (4.0%)	7 (2.1%)	10 (3.0%)	24 (2.9%)
Reason for discontinuation[a]				
Adverse event	2 (1.1%)	4 (1.2%)	2 (0.6%)	8 (1.0%)
Worsening of psoriasis	0	0	0	0
Other Adverse Event	2 (1.1%)	4 (1.2%)	2 (0.6%)	8 (1.0%)
Death	0	0	0	0
Pregnancy	0	0	0	0
Lack of Efficacy	2 (1.1%)	0	1 (0.3%)	3 (0.4%)
Lost to follow-up	1 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.4%)
Withdrawal by subject	2 (1.1%)	0	4 (1.2%)	6 (0.7%)
Non-compliance with study drug	0	2 (0.6%)	1 (0.3%)	3 (0.4%)
Protocol Violation	0	0	1 (0.3%)	1 (0.1%)
Product quality complaint	0	0	0	0
Trial site terminated by sponsor	0	0	0	0
Study terminated by sponsor	0	0	0	0
Other	0	0	0	0

a: Includes subjects who were randomized but not treated.

[TSIDS01A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDS01A.SAS] 29MAY2016, 05:59

Table 17 - Number of Subjects Who Discontinued Study Agent Through Week 48; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo → Guselkumab	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0[a]	165	329	334	828
Subjects treated with study agent	165 (100.0%)	329 (100.0%)	333 (99.7%)	827 (99.9%)
Subjects who discontinued study agent[b]	3 (1.8%)	28 (8.5%)	52 (15.6%)	83 (10.0%)
Reason for discontinuation[b]				
Adverse event	1 (0.6%)	10 (3.0%)	11 (3.3%)	22 (2.7%)
Worsening of psoriasis	0	0	5 (1.5%)	5 (0.6%)
Other Adverse Event	1 (0.6%)	10 (3.0%)	6 (1.8%)	17 (2.1%)
Death	0	0	0	0
Pregnancy	0	0	1 (0.3%)	1 (0.1%)
Lack of Efficacy	0	3 (0.9%)	12 (3.6%)	15 (1.8%)
Lost to follow-up	1 (0.6%)	3 (0.9%)	6 (1.8%)	10 (1.2%)
Withdrawal by subject	1 (0.6%)	4 (1.2%)	14 (4.2%)	19 (2.3%)
Non-compliance with study drug	0	5 (1.5%)	4 (1.2%)	9 (1.1%)
Protocol Violation	0	1 (0.3%)	1 (0.3%)	2 (0.2%)
Product quality complaint	0	0	0	0
Trial site terminated by sponsor	0	0	0	0
Study terminated by sponsor	0	0	0	0
Other	0	2 (0.6%)	3 (0.9%)	5 (0.6%)

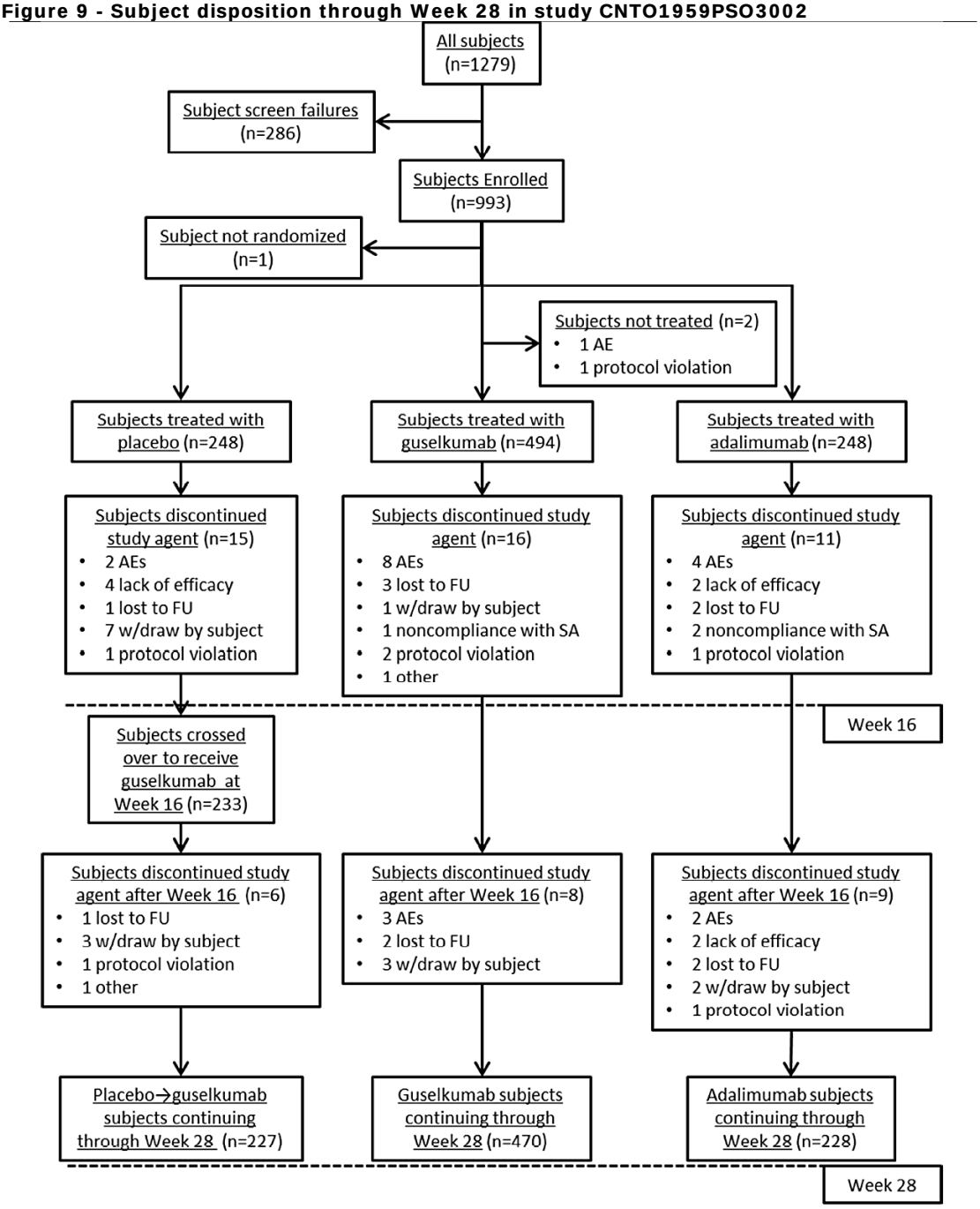
a: Placebo → Guselkumab column only includes placebo subjects crossed over to receive guselkumab.

b: Includes subjects who were randomized but not treated.

[TSIDS01B.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDS01B.SAS] 29MAY2016, 05:59

Study CNTO1959PSO3002

Figure 9 - Subject disposition through Week 28 in study CNTO1959PSO3002



Source: TSIDS01A.RTF,16JUN2016, 18:39; TSIDS01B.RTF, 16JUN2016, 18:39; TSIDS01C.RTF,16JUN2016, 18:39; TSITG01A.RTF, 16JUN2016, 18:39; TSITG01B.RTF, 16JUN2016, 18:39; TSITG01C.RTF, 21JUN2016, 10:32; LSINTX01A.RTF, 16JUN2016, 18:52

Figure 10 - Subject disposition from Week 28 through Week 48 for subjects rerandomized at Week 28 in study CNTO1959PSO3002

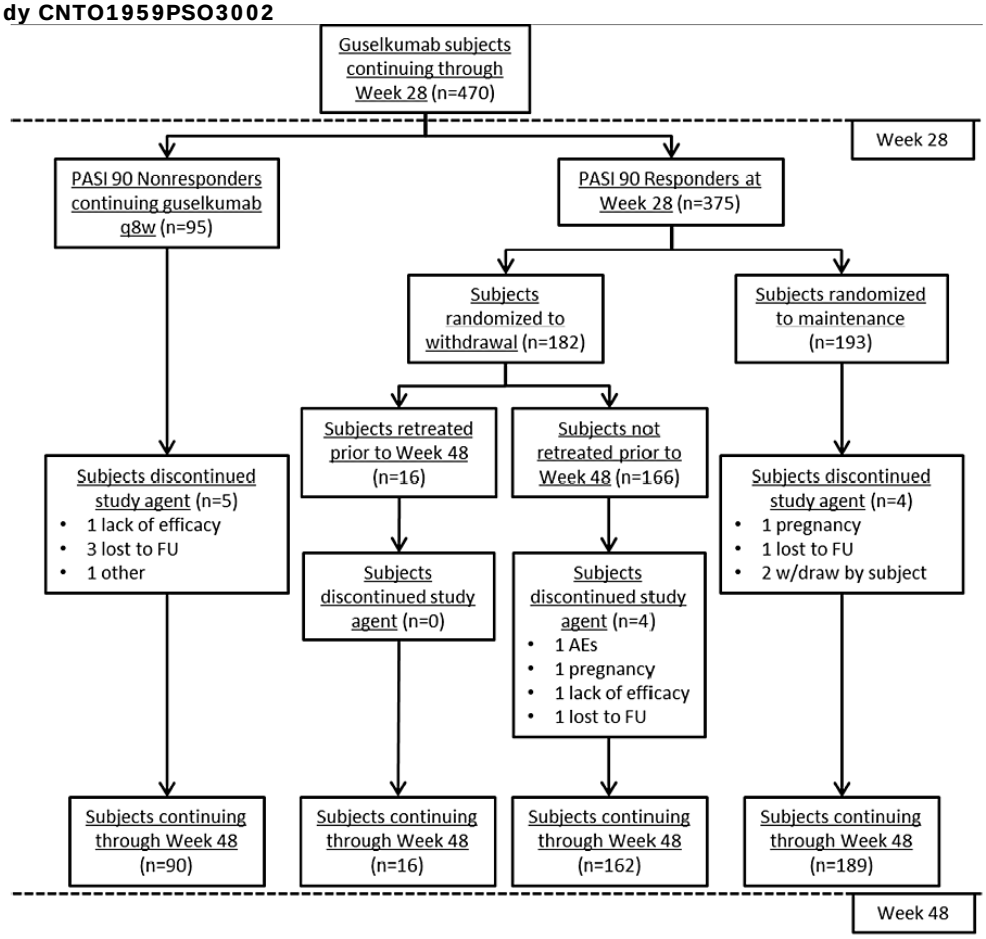


Figure 11 - Subject disposition from Week 28 through Week 48 for subjects not rerandomized at Week 28 in study CNTO1959PSO3002

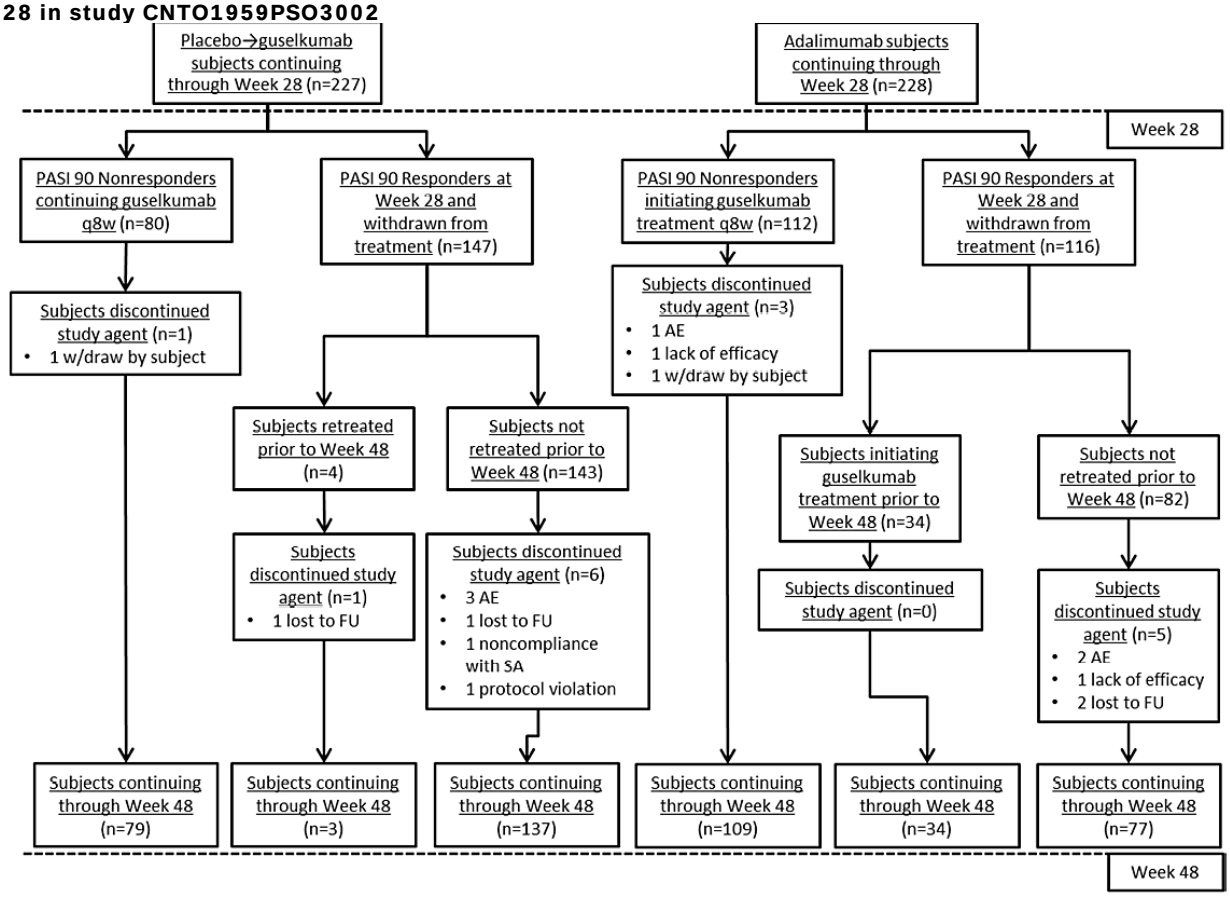


Table 18 - Summary of Subject Participation Status Through Week 48; Subjects Randomized At Week 0 (Study CNTO1959PSO3002)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects randomized at Week 0[a]	248	496	248	992
Subjects who completed study participation	223 (89.9%)	459 (92.5%)	223 (89.9%)	905 (91.2%)
Subjects who discontinued study participation	25 (10.1%)	37 (7.5%)	25 (10.1%)	87 (8.8%)
Subjects who completed safety follow-up	3 (1.2%)	6 (1.2%)	6 (2.4%)	15 (1.5%)
Subjects who did not completed safety follow-up	22 (8.9%)	31 (6.3%)	19 (7.7%)	72 (7.3%)
Withdrawal by subject	17 (6.9%)	17 (3.4%)	9 (3.6%)	43 (4.3%)
Lost to follow-up	5 (2.0%)	11 (2.2%)	9 (3.6%)	25 (2.5%)
Death	0	0	0	0
Other	0	3 (0.6%)	1 (0.4%)	4 (0.4%)

[a] Data are presented through Week 48 by the randomized treatment group at Week 0.

[TSIDS02A.RTF] [CNTO1959\PSO3002\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDS02A.SAS] 16JUN2016, 18:39

Study CNTO1959PSO3003

Figure 12 - Subject disposition in Study CNTO1959PSO3003

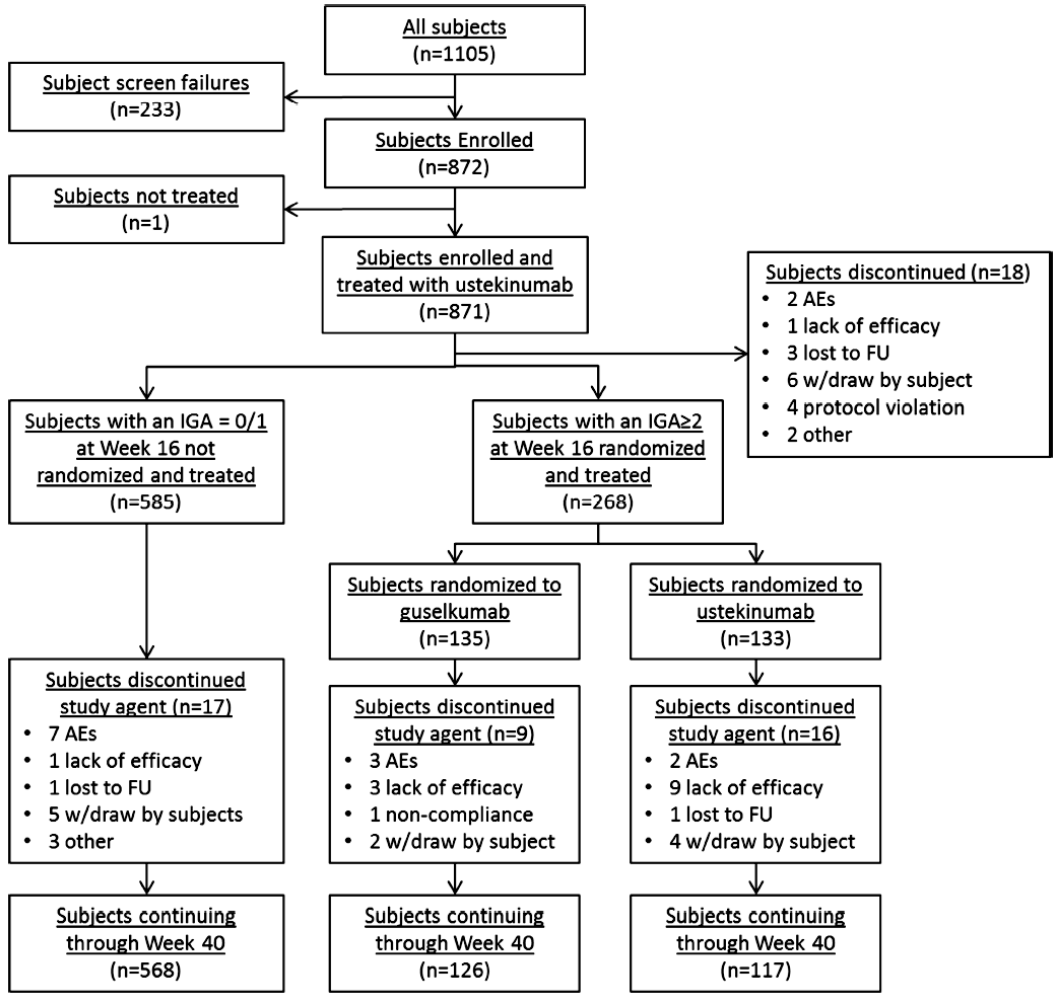


Table 19 - Number of Subjects who Discontinued Study Agent from Week 16 through Week 40; Randomized Subjects (Study CNTO1959PSO3003)

	Guselkumab	Ustekinumab	Total
Analysis set: randomized subjects	135	133	268
Randomized and treated subjects	135 (100.0%)	133 (100.0%)	268 (100.0%)
Subjects who discontinued study agent	9 (6.7%)	16 (12.0%)	25 (9.3%)
Reason for discontinuation			
Adverse event - worsening of psoriasis	0	0	0
Adverse event - other	3 (2.2%)	2 (1.5%)	5 (1.9%)
Death	0	0	0
Lack of efficacy	3 (2.2%)	9 (6.8%)	12 (4.5%)
Lost to follow-up	0	1 (0.8%)	1 (0.4%)
Non-compliance with study drug	1 (0.7%)	0	1 (0.4%)
Study drug product quality complaint	0	0	0
Trial site terminated by sponsor	0	0	0
Pregnancy	0	0	0
Withdrawal by subject	2 (1.5%)	4 (3.0%)	6 (2.2%)
Protocol violation	0	0	0
Other	0	0	0

Note: Percentages are calculated with the number of subjects randomized within each group as the denominator.

[TSIDS01A.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDS01A.SAS] 08FEB2016, 11:39

Conduct of the study

Study CNTO1959PSO3001

Database locks (DBLs) were planned to occur at Weeks 48 and 160.

Change in conduct

There were 2 amendments (issued 12 February 2015 and 17 February 2016) to the original protocol issued on 10 July 2014. The first amendment was considered substantial, and the overall reason was to address the regulatory, ethics committee, and investigator feedback. The key changes done, ensured consistency, in the assessments and the timepoints, across all the guselkumab Phase 3 psoriasis protocols.

Protocol deviations

Through Week 48, 106 (12.7%) subjects had 119 MPDs, for which the proportion were comparable across the 3 treatment groups. Twenty-six (3.1%) subjects entered the study but did not satisfy criteria. Seven (0.8%) subjects received prohibited concomitant medication. Twenty-four (2.9%) subjects received wrong treatment or incorrect dose. Fifty-five (6.6%) subjects had a total of 59 deviations that were categorized as “Other” (consent, pregnancy, storage of drugs, etc.).

The proportion of subjects missing at least 1 study agent injection (which includes both active and placebo injections) was comparable among the treatment groups. The proportion of subjects who missed at least 1 study agent injection was relatively high due to the schedule of injections occurring every 2 weeks. The proportion of subjects that missed at least 1 active injection was substantially higher in the adalimumab group because of the much larger number of total active injections required by the established dosing regimen

Study CNTO1959PSO3002

Protocol amendments

The original protocol was issued on 10 July 2014. There was 2 amendments to the protocol.

The first one (issued 12 February 2015) was considered substantial and was adopted before any study related procedures began. This amendment included the following major changes:

- Assessments describing antibodies to study agent were added at Week 16 and Week 44.
- A physical examination and weight measurement were moved to Week 100 from Week 108, and added at Week 148.
- The inclusion criteria were clarified to indicate that barrier methods should be used with a spermicidal agent if spermicidal agents are available in their locale.
- The exclusion criterion for major surgery was clarified. The text describing serious adverse event (SAE) reporting for hospitalization was edited to address a potential contradiction with this exclusion criterion.
- An exclusion criterion was added to exclude sponsor employees from participation in the study.

Amendment 2 (issued 25 June 2015) was considered substantial. The overall reason for the amendment was to restrict the use of concomitant medications for psoriasis through Week 76 instead of through Week 48.

Protocol deviations

Through Week 48, 186 (18.8%) subjects had 221 MPDs, for which the proportion were comparable across the 3 treatment groups.

Database lock: Database locks (DBL) were planned to occur at Weeks 48 and 160.

Study CNTO1959PSO3003

Two database locks (DBL) were planned for this study: one at Week 40 and one at Week 60. This CSR reports data from the Week 40 DBL. Start: 07 October 2014 (First subject screened) . To: 25 December 2015 (Last study visit for last subject).

Protocol amendments

The original protocol was issued on 03 July 2014. There was 1 amendment (issued 12 February 2015) to the protocol, which was considered substantial. The overall reason for the amendment was to address health authority, ethics committee, and investigator feedback. This amendment included the following major changes:

- Electrocardiogram (ECG) collection timepoints were added beyond Week 0 (Weeks 16, 32, and 52) to obtain additional ECG measurements for safety assessment in randomized subjects only.
- A physical examination and a urine pregnancy test were added at Week 52. An additional discontinuation criterion was added for subjects who experience signs and symptoms suspicious for reversible posterior leukoencephalopathy syndrome.
- Information was added about the presence of dry natural rubber on the ustekinumab prefilled syringe (PFS) needle cover, which might cause allergic reactions in individuals sensitive to latex.

Protocol deviations

Through Week 16, 45 (5.2%) subjects had MPDs. From Week 16 though Week 40, 20 (7.5%) randomized subjects had MPDs. (see Table below)

Table 20 - Summary of Subjects With Major Protocol Deviations From Week 16 through Week 40; Randomized Subjects (Study CNTO1959PSO3003)

	Guselkumab	Ustekinumab	Total
Analysis set: randomized subjects	135	133	268
Subjects with major protocol deviations[a,b]	13 (9.6%)	7 (5.3%)	20 (7.5%)
Developed withdrawal criteria but not withdrawn	0	0	0
Received a disallowed concomitant treatment	1 (0.7%)	1 (0.8%)	2 (0.7%)
Received wrong treatment or incorrect dose	1 (0.7%)	0	1 (0.4%)
Other	12 (8.9%)	6 (4.5%)	18 (6.7%)

[a] Subjects may appear in more than one category.
[b] The summary is based on the blinded major protocol deviation data.

[TSIDEV01A.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEV01A.SAS] 08FEB2016, 11:38

From Week 16 through Week 40, 6 (1.0%) subjects who continued to receive open-label treatment had major protocol deviations.

Baseline data

The baseline demographics and disease characteristics were generally similar across studies PSO3001, PSO3002, and PSO3003 and balanced across treatment groups within each study. The majority of subjects were male and white. The mean age and weight across studies ranged, from 43 to 44 years and 89 to 90 kg, respectively.

All subjects had moderate or severe psoriasis, based on baseline BSA, PASI, and IGA scores. The mean disease duration was about 17 years. Approximately 19% of subjects reported a diagnosis of PsA. In PSO3001 and PSO3002, the vast majority (approx. 85%) of subjects had scalp psoriasis, more than half of the subjects had nail psoriasis, and less than one-third of subjects had hand or foot psoriasis. In addition, most subjects enrolled had significant impairment in quality of life, as evidenced by a mean baseline Dermatology Life Quality Index (DLQI) score of approximately 14.5. These clinical disease characteristics are consistent with moderate to severe psoriasis and consistent with observations in previous clinical studies of biologic agents in the treatment of moderate to severe psoriasis.

Prior psoriasis medication histories of subjects enrolled in the Phase 3 studies were similar and consistent with a population of moderate to severe psoriasis subjects. In studies PSO3001 and PSO3002, approximately 30% of subjects were naïve to prior non-biologic systemic and biologic psoriasis treatments at the time of study entry. Fewer subjects in PSO3003 used non-biologic or biologic systemic therapies and 41.2% were naïve to any nonbiologic or biologic systemic psoriasis therapies.

Table 21 - Summary of Demographic and Disease Characteristics; Randomized Subjects in the Guselkumab Phase 3 Psoriasis Program

	PSO3001	PSO3002	PSO3003
Randomized subjects (N)	837	992	871a
Demographic characteristics			
Sex, % Male	608 (72.6%)	692 (69.8%)	566 (65.0%)
Race, % White	684 (81.7%)	814 (82.1%)	747 (85.8)
Mean age (SD), years	43.7 (12.72)	43.5 (12.18)	43.1 (13.21)
Mean weight (SD), kg	89.6 (21.75)	88.7 (20.68)	88.3 (21.96)
Disease characteristics			
Mean disease duration, years	17.5	17.79	16.76
PsA	156 (18.6%)	179 (18.0%)	128 (14.7%)
Scalp psoriasis	736 (87.9%)	840 (84.7%)	nc
Nail psoriasis	491 (58.7%)	558 (56.3%)	nc
Hand or foot psoriasis	245 (29.3%)	256 (25.8%)	nc
BSA %, mean (SD)	27.9 (16.70)	28.5 (16.52)	28.2 (16.76)
PASI score, mean (SD)	21.85 (9.154)	21.75 (8.638)	21.61 (9.237)
IGA score			
mild (2)	3 (0.4%)	1 (0.1%)	1 (0.1%)
moderate (3)	624 (74.6%)	766 (77.2%)	694 (79.7%)
severe (4)	210 (25.1%)	225 (22.7%)	176 (20.2%)
DLQI, mean (SD)	14.0 (7.33)	14.9 (7.00)	14.5 (7.18)
PSSD symptom score (0-100), mean (SD)	53.0 (25.03)	55.1 (25.56)	50.6 (24.68)
PSSD sign score (0-100), mean (SD)	56.9 (21.34)	57.6 (21.79)	60.7 (20.42)

[a]Subjects enrolled and treated at Week 0 in study PSO3003. Subjects in this study were not randomized until Week 16.
Abbreviations: kg=kilogram; BSA=body surface area; PsA=psoriatic arthritis; PASI=Psoriasis Area and Severity Index; IGA=Investigator's Global Assessment; DLQI=Dermatology Life Quality of Life; PSSD=Psoriasis Symptom and Sign Diary; nc=not collected; SD=standard deviation

Numbers analysed

Study CNTO1959PSO3001

The primary efficacy population in this study included all subjects randomized at Week 0 (randomized analysis set). For all efficacy analyses, subjects were analyzed according to the randomized treatment group to which they were assigned, regardless of the treatment they actually received. Of note, only 1 subject was randomized but not treated in the study; the subject had been randomized to the adalimumab treatment group . This subject was included in the efficacy analyses.

A total of 49 subjects were excluded from the per-protocol analysis. No subjects in the placebo group were excluded from the per-protocol population. Twelve (3.6%) subjects were assigned to the guselkumab group; the remaining 37 (11.1%) subjects were assigned to the adalimumab group. In both treatment groups, the majority of subjects excluded from the analyses were due to not receiving the required active study agent.

Table 22 - Summary of Subjects per Analysis set; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0	174	329	334	837
Efficacy Analysis Set	174 (100.0%)	329 (100.0%)	334 (100.0%)	837 (100.0%)
Per-protocol Analysis Set	174 (100.0%)	317 (96.4%)	297 (88.9%)	788 (94.1%)
Safety Analysis Set	174 (100.0%)	329 (100.0%)	333 (99.7%)	836 (99.9%)

[TSITG01A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSITG01A.SAS] 24JUN2016, 11:42

Study CNTO1959PSO3002

The primary efficacy population in this study included all subjects randomized at Week 0 (randomized analysis set). For all efficacy analyses, subjects were analyzed according to the randomized treatment group to which they were assigned, regardless of the treatment they actually received. Of note, 2 subjects were randomized but not treated in the study; both in the guselkumab treatment group. For subjects randomized to placebo, only subjects who crossed over to receive guselkumab 100 mg (placebo→guselkumab) at or after Week 16 were included in the efficacy summaries for the visits after Week 16. Efficacy data for these crossover subjects were not used for any formal comparisons.

Study CNTO1959PSO3003

The primary efficacy population in this study includes all subjects who were randomized at Week 16 (randomized analysis set). Subjects were analysed according to their randomized treatment group for all efficacy analyses, regardless of the treatment they actually received. In addition, selected efficacy analyses were performed based on enrolled and treated subjects, and nonrandomized subjects.

Table 23 - Summary of Subjects per Analysis Set; All Enrolled Subjects (Study CNTO1959PSO3003

		Randomized		
	Ustekinumab Open-label	Guselkumab	Ustekinumab	Total
Status				
Week 0				
Enrolled	872	-	-	872
Enrolled and treated	871	-	-	871
Week 16				
Randomized	-	135	133	268
Randomized and treated	-	135	133	268
Per-protocol	-	127	128	255
Non-randomized and continued to receive open-label treatment	585	-	-	585

[TSITG02.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSITG02.SAS] 08FEB2016, 11:39

Outcomes and estimation

Outcomes of studies PSO3001 and PSO3002

Psoriasis improvement through week 24

Studies PSO3001 and PSO3002 demonstrated robust efficacy of guselkumab, with both studies meeting their co-primary and all multiplicity adjusted major secondary endpoints through Week 24 (all p<0.001). At Week 16, a significantly greater proportion of subjects in the guselkumab group achieved an IGA 0 and IGA 0/1 scores, and PASI 100, PASI 90, and PASI 75 responses compared with the placebo group and for IGA 0/1, PASI 90, and PASI 75 compared to the adalimumab group . At Week 24, a significantly greater proportion of subjects in the guselkumab group achieved an IGA 0, IGA 0/1, and PASI 100, PASI 90, and PASI 75 responses compared with the adalimumab group.

IGA scores and PASI responses were consistent for each treatment group in both studies and comparable across the 2 studies, thus the magnitude of treatment differences was consistent between the 2 studies for guselkumab compared with placebo and adalimumab.

The onset of clinical efficacy, measured by IGA 0/1 and PASI 90 response, occurred as early as Week 2 in both studies (PSO3001 and PS03002). Additionally, by Week 8 in both studies, guselkumab treatment responses also separated from those of adalimumab. The response separation between guselkumab and adalimumab continued to increase and reached a maximum around Week 16 and 20 for IGA 0/1 and PASI 90 response, respectively, and was maintained through Week 24. Consistent results were also observed for IGA 0 and PASI 100.

Table 24 - Efficacy Endpoints for Psoriasis Improvement in Studies PSO3001 and PSO3002

	PSO3001			PSO3002		
	Placebo	Guselkumab[a]	Adalimumab[b]	Placebo	Guselkumab[a]	Adalimumab[b]
Number of subjects	174	329	334	248	496	248
Week 16						
IGA 0	2 (1.1%)	157 (47.7%)	88 (26.3%)	2 (0.8%)	215 (43.3%)	71 (28.6%)
p-value		<0.001	nc		<0.001	nc
IGA 0/1	12 (6.9%)	280 (85.1%)	220 (65.9%)	21 (8.5%)	417 (84.1%)	168 (67.7%)
p-value		<0.001[c]	<0.001[d]		<0.001[c]	<0.001[d]
PASI 100	1 (0.6%)	123 (38.1%)	57 (17.4%)	2 (0.8%)	169 (34.1%)	51 (20.6%)
p-value		<0.001	nc		<0.001	nc
PASI 90	5 (2.9%)	241 (73.3%)	166 (49.7%)	6 (2.4%)	347 (70.0%)	116 (46.8%)
p-value		< 0.001[c]	< 0.001[d]		< 0.001[c]	< 0.001[d]
PASI 75	10 (5.7%)	300 (91.2%)	244 (73.1%)	20 (8.1%)	428 (86.3%)	170 (68.5%)
p-value		< 0.001	<0.001[d]		< 0.001	<0.001[d]
Week 24						
IGA 0	na	173 (52.6%)	98 (29.3%)	na	257 (51.8%)	78 (31.5%)
p-value			<0.001[d]			<0.001[d]
IGA 0/1	na	277 (84.2%)	206 (61.7%)	na	414 (83.5%)	161 (64.9%)
p-value			<0.001[d]			<0.001[d]
PASI 100	na	146 (44.4%)	83 (24.9%)	na	219 (44.2%)	66 (26.6%)
p-value			<0.001			<0.001
PASI 90	na	264 (80.2%)	177 (53.0%)	na	373 (75.2%)	136 (54.8%)
p-value			<0.001[d]			<0.001[d]
PASI 75	na	300 (91.2%)	241 (72.2%)	na	442 (89.1%)	176 (71.0%)
p-value			<0.001			<0.001

Data are presented as number of subjects (%).

[a] p-values are for comparisons between guselkumab and placebo
[b] p-values are for comparisons between guselkumab and adalimumab
[c] p-values are for the comparisons for the co-primary endpoints
[d] p-values are for the comparisons for major secondary endpoints

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; na=not applicable; nc=not calculated

Psoriasis Improvement through Week 48

Study 3001 – continuous treatment

Study PSO3001 evaluated the efficacy of guselkumab compared with adalimumab through Week 48 in the overall population, and therefore provides the best evidence of persistence of efficacy resulting from continuous treatment.

Beginning at Week 8 and continuing through Week 48, guselkumab-treated subjects maintained higher rates of all 4 PASI responses (PASI 100, PASI 90, PASI 75, PASI 50) compared with adalimumab-treated subjects. For PASI 90 responses (Figure 13), the maximum efficacy in the guselkumab group and maximum separation from the adalimumab group appeared to occur by Week 20 and was maintained through Week 48. Comparable results were observed for IGA 0 (Figure 14). Assessed by complete psoriasis clearance (PASI 100 response and IGA 0), guselkumab demonstrated a high level of efficacy as evident at Week 48 with 47.4% and 50.5% of subjects in the guselkumab group achieving a PASI 100 response and IGA 0, respectively.

These results indicate that high levels of clinical response were maintained with continuous guselkumab treatment administered q8w.

Figure 13 - Percent of Subjects Achieving PASI 90 Response Through Week 48 by Visit; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

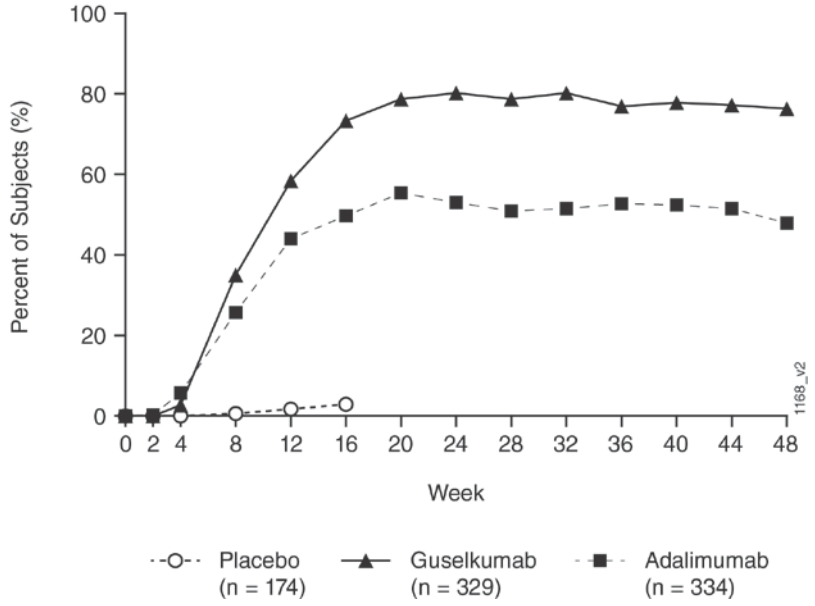


Figure 14 - Percent of Subjects Who Achieved IGA Score of Cleared (0) Through Week 48 by Visit; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

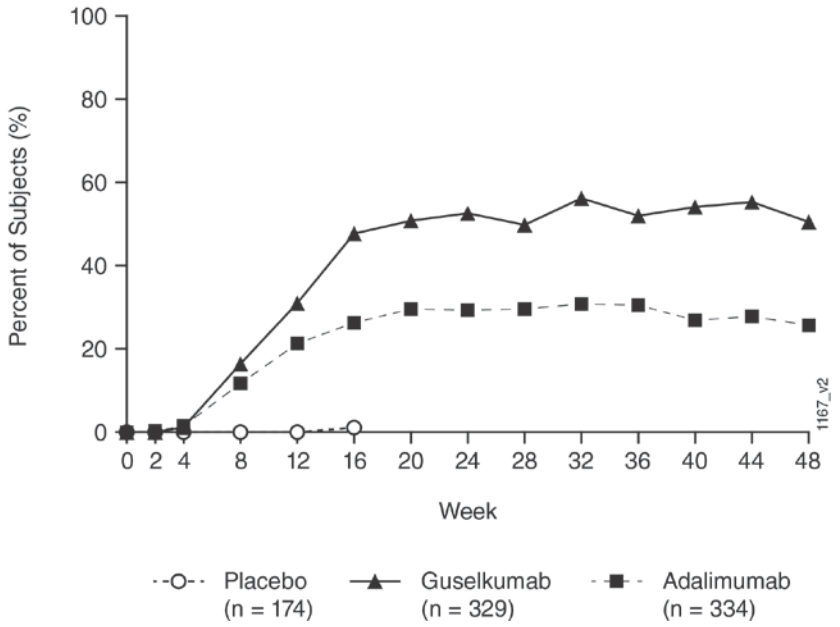


Table 25 - Efficacy Endpoints for Psoriasis Improvement at Week 48 in Study CNTO1959PSO3001

	Guselkumab	Adalimumab[a]
Randomized subjects	329	334
IGA 0	166 (50.5%)	86 (25.7%)
p-value		*<0.001*[b]
IGA 0/1	265 (80.5%)	185 (55.4%)
p-value		*<0.001*[b]
PASI 100	156 (47.4%)	78 (23.4%)
p-value		*<0.001*
PASI 90	251 (76.3%)	160 (47.9%)
p-value		*< 0.001*[b]
PASI 75	289 (87.8%)	209 (62.6%)
p-value		*< 0.001*

[a] p-values are for comparisons between guselkumab and adalimumab.
[b] p-values are for the comparisons for major secondary endpoints.
PASI=Psoriasis Area and Severity Index; IGA=Investigator's Global Assessment

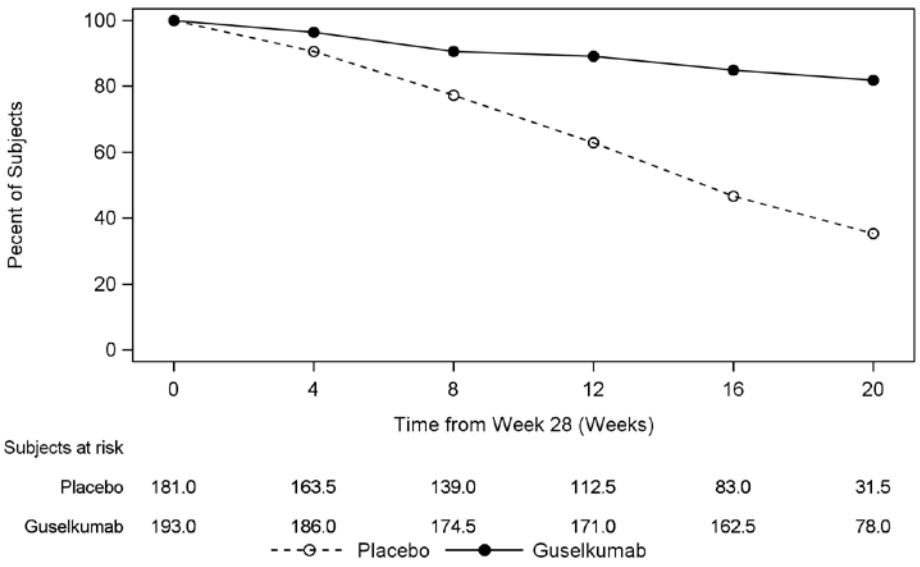
Study 3002 - maintenance of response

Subjects originally randomized to the guselkumab group who had achieved a PASI 90 response at Week 28 were rerandomized to either continue guselkumab treatment (maintenance group) or be withdrawn from guselkumab treatment; ie, receive placebo (withdrawal group). A life-table estimates analysis was utilized in which subjects were counted as having lost a PASI 90 response from the visit at which it was first lost and then for all subsequent visits as well. Among subjects rerandomized at Week 28, PASI 90 response was significantly better maintained through Week 48 among subjects continuing to receive guselkumab than it was among subjects in whom guselkumab treatment was withdrawn (Figure 15). Specifically, among PASI 90 responders randomized to withdrawal group, loss of PASI 90 response was evident as early as 4 weeks after withdrawal of therapy (Week 28) with the

median time to loss of PASI 90 of 15.2 weeks. At Week 48, a significantly greater proportion of subjects in the guselkumab maintenance group were PASI 90 responders compared with the withdrawal group (88.6% vs 36.8% p<0.001).

In addition, subjects in the placebo→guselkumab group who were PASI 90 responders at Week 28 and withdrawn from therapy showed a similar loss of efficacy.

Figure 15 - Life-Table Estimate of Percent of Subjects Maintaining PASI 90 Response; Subjects Randomized At Week 28 (Study CNTO1959PSO3002)



Study 3002 - response to retreatment

Study PSO3002 also evaluated the efficacy of re-treatment with guselkumab. Twenty subjects who experienced loss of therapeutic effect (ie, loss of ≥ 50% of their Week 28 PASI improvement) after withdrawal from therapy were followed for at least 4 weeks after reinitiating guselkumab. Within 4 weeks of re-initiation of therapy, the majority of subjects (65%, 13/20) achieved at least a PASI 50 response. However, the number of subjects who were re-treated 8 weeks or longer prior to Week 48 was small and thus limits the interpretation of the results for re-treatment with guselkumab.

Study 3002 - psoriasis improvement for PASI 90 nonresponders at week 28

Subjects randomized to adalimumab who were PASI 90 nonresponders at Week 28 initiated the guselkumab 100 mg dose regimen (guselkumab 100 mg SC at Weeks 28 and 32, followed by q8w thereafter) from Week 28 through Week 48. The proportion of subjects with a PASI 90 response increased within 4 weeks of initiating guselkumab 100 mg at Week 28 and was 66.1% by Week 48. A similar trend was observed for IGA scores through Week 48.

With continued treatment with guselkumab, some subjects who were PASI 90 nonresponders at Week 28 in both the placebo→guselkumab and guselkumab groups showed improvement in PASI response through Week 48, with 60.0% of subjects in the placebo→guselkumab and 35.8% of subjects in the guselkumab group achieving a PASI 90 response at Week 48.

Improvement in Regional Measures of Psoriasis

Consistent improvements were observed in scalp psoriasis, nail psoriasis, and hand or foot psoriasis in the guselkumab group compared with the placebo group at Week 16 across studies PSO3001 and PSO3002 for subjects with an ss-IGA, f-PGA, and/or hf-PGA score ≥ 2 at baseline or with a NAPSI score >0 at baseline . In addition, in both studies, a significantly higher proportion of guselkumab subjects had scalp psoriasis and hand and foot psoriasis improvement compared with the adalimumab group at Week 24. Although guselkumab treatment resulted in substantial improvement of nail psoriasis, the effects observed were not significantly different between the guselkumab and adalimumab groups in either study as measured by f-PGA or NAPSI at Week 24.

At Week 48 in study PSO3001:

- A significantly (p=0.038) greater proportion of guselkumab subjects (74.7%) achieved an f-PGA score of 0 or 1 than adalimumab subjects (61.8%).
- Subjects in the guselkumab group had a greater mean percent improvement in NAPSI score comparable to subjects in the adalimumab group.
- Subjects in the guselkumab group had significantly greater (p<0.001) differences in ss-IGA scores and at least a 2-grade improvement from baseline compared with adalimumab.
- Guselkumab treatment produced a significantly higher proportion of subjects with hf-PGA score of 0 or 1 and at least a 2-grade improvement from baseline than adalimumab (p=0.045).

In study PSO3002, subjects who were PASI 90 responders at Week 28 and rerandomized to continue guselkumab at Week 28 showed continued improvement in f-PGA and NAPSI scores at Week 48 and maintained their ss-IGA and hf-PGA scores at Week 48.

Table 26 - Efficacy Endpoints for Regional Psoriasis in Studies PSO3001 and PSO3002

	PSO3001			PSO3002		
	Placebo	Guselkumab[a]	Adalimumab[b]	Placebo	Guselkumab[a]	Adalimumab[b]
Week 16						
ss-IGA, n[c]	145	277	286	202	408	194
ss-IGA 0/1[d]	21 (14.5%)	231 (83.4%)	201 (70.3%)	22 (10.9%)	329 (80.6%)	130 (67.0%)
p-value		<0.001[e]	nc		<0.001[e]	nc
f-PGA, n[c]	88	174	173	123	246	124
f-PGA 0/1	14 (15.9%)	68 (39.1%)	88 (50.9%)	18 (14.6%)	128 (52.0%)	74 (59.7%)
p-value		<0.001	nc		<0.001	nc
NAPSI, n[c]	99	194	191	140	280	140
% improvement	-0.93 (57.893)	34.37 (42.448)	37.95 (53.872)	1.82 (53.825)	39.61 (45.648)	46.92 (48.091)
p-value		<0.001	nc		<0.001	nc
hf-PGA, n[c]	43	90	95	63	114	56
hf-PGA 0/1[d]	6 (14.0%)	66 (73.3%)	53 (55.8%)	9 (14.3%)	88 (77.2%)	40 (71.4%)
p-value		<0.001	nc		<0.001	nc
Week 24						
ss-IGA, n[c]		277	286		408	194
ss-IGA 0/1[d]	na	234 (84.5%)	198 (69.2%)	na	348 (85.3%)	131 (67.5%)
p-value			<0.001			<0.001
f-PGA, n[c]		174	173		246	124
f-PGA 0/1	na	98 (56.3%)	108 (62.4%)	na	154 (62.6%)	83 (66.9%)
p-value			0.176			0.376
NAPSI, n[c]		194	191		280	140
% improvement	na	49.78 (44.156)	49.42 (60.042)	na	54.98 (46.804)	53.69 (49.456)
p-value			0.739			0.667
hf-PGA, n[c]		90	95		114	56
hf-PGA 0/1[d]	na	71 (78.9%)	54 (56.8%)	na	93 (81.6%)	37 (66.1%)
p-value			0.001			0.046
Week 48						
ss-IGA, n[c]		277	286			
ss-IGA 0/1[d]	na	217 (78.3%)	173 (60.5%)	na	na	na
p-value			<0.001			
f-PGA, n[c]		174	173			
f-PGA 0/1	na	130 (74.7%)	107 (61.8%)	na	na	na
p-value			0.038			
NAPSI, n[c]		194	191			
% improvement	na	68.14 (42.998)	61.37 (49.204)	na	na	na
p-value			0.229			
hf-PGA, n[c]		90	95			
hf-PGA 0/1[d]	na	68 (75.6%)	59 (62.1%)	na	na	na
p-value			0.045			

Data are presented as number of subjects (%) or mean ± standard deviation.
[a] p-values are for comparisons between guselkumab and placebo
[b] p-values are for comparisons between guselkumab and adalimumab
[c] Includes only subjects with ss-IGA, f-PGA, hf-PGA score ≥2, and/or NAPSI score >0 at baseline.
[d] Includes only subjects also achieving ≥2-grade improvement in ss-IGA and/or hf-PGA.
[e] p-values are for the comparisons for major secondary endpoints.
f-PGA=fingernail PGA; hf-PGA=Physician's Global Assessment of Hands and/or Feet; NAPSI=Nail Psoriasis Severity Index; ss-IGA=Scalp Specific Investigator Global Assessment; na= not applicable; nc=not calculated

Improvement in Patient-reported Outcomes and Health-related Quality of Life Measures

Key patient-reported outcomes used to assess the efficacy of guselkumab in PSO3001 and PSO3002 included the PSSD and the DLQI. Additional patient-reported outcome efficacy measures used only in study PSO3002 included the 36-item Short Form Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), and Work Limitations Questionnaire (WLQ).

Psoriasis Symptom and Sign Diary

The PSSD is a PRO questionnaire designed and validated by the Applicant to measure the severity of psoriasis symptoms (itch, burning, stinging, skin tightness, and pain) and signs (skin dryness,

cracking, scaling, shedding or flaking, redness, and bleeding) using a 0 to 10 numerical rating scale for the assessment of treatment benefit. Two summary scores are derived: the psoriasis symptom score and the psoriasis sign score. Summary scores range from 0 to 100 and a higher score indicates more severe disease.

Across both studies PSO3001 and PSO3002, and consistent with the improvement observed in the physician-assessments (PASI and IGA), significant improvements in PSSD summary scores were observed in the guselkumab group compared with the placebo group at Week 16 (all $p<0.001$. The magnitude of improvements of PSSD scores including individual symptom or sign scale scores from baseline within treatment groups was consistent between the 2 studies. Significantly better improvements in PSSD scores were also observed in the guselkumab group compared with the adalimumab group at Week 24. Most importantly, the proportions of subjects treated with guselkumab that had clinically meaningful improvements (i.e. $\geq$ 40 points) in symptom and sign scores at Week 24 were significantly higher compared to subjects treated with adalimumab, as were the proportions of guselkumab-treated subjects free of all symptoms and signs of psoriasis (i.e. sign and symptom scores =0).

At Week 48 of study PSO3001, subjects in the guselkumab group had a significantly greater improvement in PSSD summary scores and in each individual PSSD symptom scale and in each individual PSSD sign scale score than subjects in the adalimumab group.

In addition, through Week 48 in study PSO3002, improvements in PSSD scores were maintained among subjects who were rerandomized to guselkumab at Week 28, while PSSD improvements declined among those subjects rerandomized to the placebo group and had treatment withdrawn.

Dermatology Life Quality Index

The DLQI is a quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is a 10-item PRO questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30. A higher score indicates more severe disease while a score of 0 or 1 represents no impact of skin disease on health related quality of life.

Across both studies (PSO3001 and PSO3002) significant improvements in DLQI scores were observed in the guselkumab group compared with the placebo group at Week 16 (all $p<0.001$) and numerically greater improvements compared with the adalimumab group at Week 24 . In particular, a significantly greater proportion of subjects in the guselkumab groups of both studies had a DLQI score of 0 or 1 (indicating no impact of skin disease on subjects' health-related quality of life) compared with subjects in the placebo group at Week 16, and adalimumab at Week 24 (all $p<0.001$). In study PSO3001, a significantly greater proportion of subjects in the guselkumab group achieved a DLQI score of 0 or 1, compared with the adalimumab group at Week 48. In study PSO3002, improvements in DLQI were maintained through Week 48 among subjects who were randomized to guselkumab (ie, maintenance group) at Week 28, while DLQI improvements declined among those subjects randomized to the placebo group and had treatment withdrawn.

Other Health-related Quality of Life Measures

In study PSO3002, the SF-36, HADS, and WLQ were completed by subjects at the site and captured electronically.

- The guselkumab group had significant improvements from baseline in the SF-36 physical (5.462 vs 0.941, $p<0.001$) and mental (5.659 vs 0.568, $p<0.001$) component summary scores at

Week 16 compared with the placebo group. The proportion of subjects with a clinically meaningful improvement of 5 or more from baseline in SF-36 physical and mental component summary scores at Week 16 was significantly greater for subjects in the guselkumab group compared with the placebo group.

- At Week 16, subjects in the guselkumab group had a significantly greater mean improvement from baseline in the HADS anxiety (-1.1 vs -0.2, p<0.001) and depression (-1.6 vs -0.1, p<0.001) scores as compared with the placebo group. Among subjects with baseline hospital anxiety score ≥ 8 (instrument definition of anxiety) or with baseline depression score ≥ 8 (instrument definition of depression), the proportions of subjects with a hospital anxiety score <8 or depression score <8 at Week 16 were significantly greater for subjects in the guselkumab group compared with the placebo group.

- At Week 16, subjects in the guselkumab group had significantly greater improvement in all scores of the WLQ compared with the placebo group: physical demand score (-7.5 vs 0.4, p<0.001); time management score (-6.0 vs 0.1 p=0.002); mental-interpersonal score (-5.3 vs -0.7, p=0.002); output demand score (-5.8 vs -2.2, p=0.026).

Ancillary analyses of studies 3001 and 3002 - improvement in psoriasis across subpopulations

The consistency of the co-primary and selected major secondary endpoints (IGA 0/1 and PASI 90 at Week 16 and Week 24, and IGA 0 at Week 24) was examined across relevant subpopulations of subjects in studies PSO3001 and PSO3002.

- Baseline demographics; sex, race, baseline age, baseline weight, baseline weight by quartiles, body mass index, and geographic location.

- Baseline disease characteristics; age at diagnosis, psoriasis disease duration, baseline PASI, baseline IGA, baseline BSA, baseline DLQI, presence of PsA.

- Psoriasis medication history; use of phototherapy (UVB or PUVA), non-biologic systemic therapies, biologic systemic therapies, either non-biologic or biologic systemic therapies, anti-TNFα agents (etanercept, infliximab), IL-12/23 inhibitors (ustekinumab, briakinumab), IL-17 inhibitors (secukinumab, ixekizumab, or brodalumab), subjects who had an inadequate response to, were intolerant to, or had a contraindication to non-biologic systemic therapies (PUVA, MTX, cyclosporine), biologic systemic therapies (etanercept, infliximab, ustekinumab) or etanercept.

Subgroup analyses (proportion differences and 95% CI) were performed based on the individual study (PSO3001 and PSO3002) data. To increase precision, subgroup analyses were also performed based on the pooled data from these 2 studies.

In each individual study, among all the subgroups with a reasonable sample size for evaluation (ie, sample size is ≥ 10 subjects in both groups for placebo comparisons and ≥ 20 subjects in both groups for adalimumab comparisons), guselkumab showed a numerically higher response than placebo (Week 16) or adalimumab (Week 24) treatment across all demographics, baseline disease characteristics, and psoriasis medication history. Similar results were observed for the **pooled data** from PSO3001 and PSO3002. While modest variability of performance was evident for some subgroups, particularly for those with a small sample size, these results demonstrate that guselkumab was highly effective across all of the subpopulations analyzed.

Impact of Body Weight

Serum guselkumab concentrations were affected by body weight. Subjects of higher body weight at baseline (>90 kg) had approximately 30% to 36% lower mean steady-state trough serum guselkumab

concentrations compared with subjects of lower body weight (≤ 90 kg). Although the impact of weight on PK was considered modest, several analyses were performed to examine the impact of body weight on PASI and IGA response rates for subjects that received the proposed guselkumab dose regimen (ie, 100 mg at Weeks 0, 4 and q8w). In studies PSO3001 and PSO3002, subjects in the guselkumab group consistently achieved higher clinical responses compared with both the placebo group at Week 16 and the adalimumab group at Week 24 and Week 48 across all weight strata. Clinical responses were modestly lower in the >90 kg subgroup compared with the ≤ 90 kg subgroup through Week 24, particularly for the higher level of responses (eg, PASI 100). However, differences in the response rates between the 2 weight subgroups decreased over time and were comparable at Week 48 in the PSO3001 study.

Using the pooled data from PSO3001 and PSO3002 at Week 16, subgroup analyses showed that response rate treatment effects (guselkumab minus placebo) for IGA 0/1 were consistent across all baseline weight quartiles. Response rates for IGA 0/1 at Week 24, using pooled data from PSO3001 and PSO3002, were slightly lower (approximately 5%) in subjects >90 kg than in those ≤ 90 kg. Modeling and simulation results of the pooled PSO2001, PSO3001, and PSO3002 data predicted that the effect of weight on response at Week 16 and Week 28 would be modest. For example, the model-predicted efficacy response rates of the 100 mg q8w dose regimen at Week 16 were approximately 6% lower in subjects >90 kg compared with subjects ≥ 90 kg. However, the flat slope of the simulated dose response curve beyond the 100 mg dose for subjects in both body weight categories suggested that a weight-based dose adjustment would not result in a substantial change in response rates, and therefore is not warranted.

Outcomes of study PSO3003

In study PSO3003, efficacy analyses based on the number of visits (of the 4 visits between Week 28 and Week 40) at which subjects achieved predefined high levels of IGA or PASI responses were utilized primarily to allow for an evaluation of the consistency of response over time. In addition, this approach accounts for the effects of peak and trough drug exposure variation between the 2 drugs (guselkumab and ustekinumab) over the 4-month dosing interval and corresponding 4 visits.

Subjects who were ustekinumab inadequate responders (defined as having an IGA score ≥ 2 at Week 16) had significantly better efficacy following the switch to guselkumab compared to the group that remained on ustekinumab. All primary and multiplicity-adjusted major secondary endpoints of study PSO3003 were met (p≤ 0.001 for all comparisons). Efficacy analyses demonstrated that the guselkumab group achieved clinical responses approximately twice as often as the ustekinumab group.

In addition to analyses based on the number of visits at which subjects achieved predefined response levels, differences in response rates over time, which are generally more intuitive to clinicians, were also analyzed. Differences in PASI 90 response rate between guselkumab and ustekinumab treated subjects favoring guselkumab were noted as early as 4 weeks after subjects were randomized at Week 16 (ie, Week 20), and then continued to increase through Week 40. The proportion of randomized subjects in the guselkumab group with an IGA 0/1 and ≥ 2 grade improvement from Week 16 demonstrated a similar result.

Table 27 - IGA and PASI Results; Randomized Subjects (Study PSO3003)

	Guselkumab	Ustekinumab
Analysis set: randomized subjects	135	133
Primary endpoint		
Number of visits‡ at which subjects achieved IGA 0/1	1.5 ± 1.57*	0.7 ± 1.26

and ≥2-grade improvement (relative to Week 16) from Week 28 through Week 40		
Major secondary endpoints		
Number of visits‡ at which subjects achieved PASI 90 between Week 28 and Week 40	2.2 ± 1.69*	1.1 ± 1.53
Number of visits‡ at which subjects achieved IGA 0 between Week 28 and Week 40	0.9 ± 1.34*	0.4 ± 1.06
Proportion of subjects with IGA 0/1 and ≥ 2-grade improvement (relative to Week 16) at Week 28	42 (31.1)*	19 (14.3)
Other secondary endpoint		
Proportion of subjects with PASI 90 response at Week 28	65 (48.1)*	30 (22.6)

* p≤0.001
‡ Maximum number of visits from Week 28 through Week 40 = 4.
IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index;

The guselkumab group also demonstrated a significantly greater improvement in patient-reported outcomes (DLQI and PSSD) compared with the ustekinumab group. The mean number of visits at which randomized subjects had a DLQI score of 0 or 1 from Week 28 through Week 40 was significantly higher for subjects in the guselkumab group compared with the ustekinumab group (1.4 visits and 0.7 visits, respectively; p=0.002). The mean number of visits at which randomized subjects had a PSSD symptom score of 0 from Week 28 through Week 40 was significantly higher for subjects in the guselkumab group compared with the ustekinumab group (0.6 visits and 0.3 visits, respectively; p=0.028).

These study results demonstrate that psoriasis subjects who had not achieved a "cleared" or "minimal" response on ustekinumab by Week 16 derived significant benefit from switching to guselkumab relative to remaining on ustekinumab.

Figure 16 - Percent of Subjects Who Achieved PASI 90 Response from Week 16 Through Week 40 by Visit; Randomized Subjects (Study CNTO1959PSO3003)

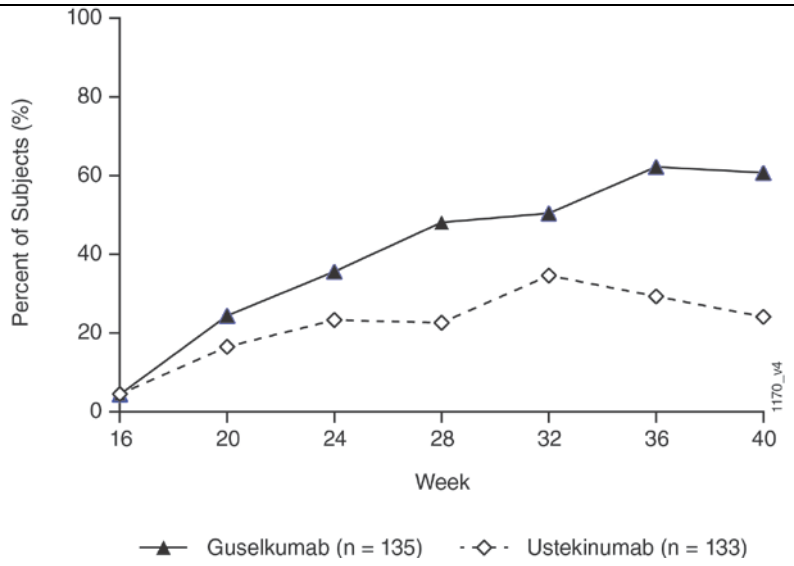
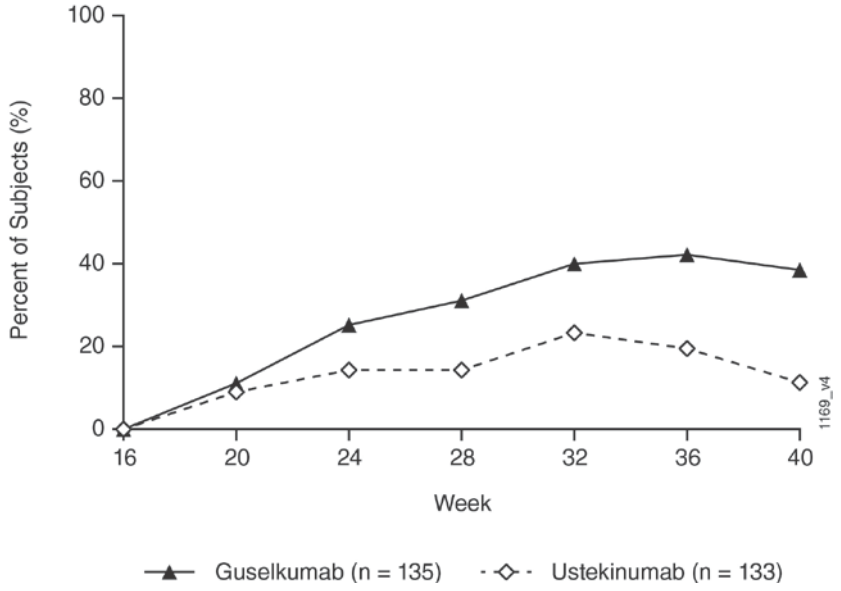


Figure 17 - Percent of Subjects Who Achieved IGA Score of Cleared (0) or Minimal (1) and at least 2 Grade Improvement from Week 16 Through Week 40 by Visit; Randomized Subjects (Study CNTO1959PSO3003)



Impact of immunogenicity on the efficacy of guselkumab

In the Phase 2 study PSO2001 and Phase 3 studies PSO3001, PSO3002, and PSO3003, the development of antibodies to guselkumab and the titer of antibodies to guselkumab were not associated with a reduction in the clinical efficacy of guselkumab. However, the small number of antibody positive subjects observed in these studies limits a definitive conclusion of the impact of antibodies to guselkumab on clinical efficacy.

Relevant data from studies PSO3001 and PSO3002 were also pooled and analyzed to further evaluate the impact of antibodies to guselkumab on the efficacy of guselkumab. Consistent with the results from the individual studies, the development of antibodies to guselkumab and peak titers did not appear to be associated with a reduction in the efficacy of guselkumab.

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 28 - Table Summary of efficacy for trial PSO2001

TITLE: A phase 2 multicenter, randomized, placebo- and active-comparator-controlled, dose-ranging trial to evaluate CNTO 1959 for the treatment of subjects with moderate to severe plaque-type psoriasis	
study identifier	**CNTO1959PSO2001**

design	randomized, placebo- and active-comparator-controlled, dose-ranging trial		
	duration of main phase: duration of extension phase duration of follow-up phase		week 16 week 40 week 52
hypothesis	superiority to placebo, non-inferiority and superiority to adalimumab		
treatments groups	placebo		s.c. placebo for 16 weeks, switch to guselkumab 100 mg q8w from week 16 through week 40, n=42
	guselkumab 5 mg q12w		s.c. guselkumab 5 mg at weeks 0 and 4 then every 12 weeks, for 52 weeks, n=41
	guselkumab 15 mg q8w		s.c. guselkumab 15 mg every 8 weeks, for 52 weeks, n=41
	guselkumab 50 mg q12w		s.c. guselkumab 50 mg at week 0 and week 4 then q12w, for 52 weeks, n=42
	guselkumab 100 mg q8w		s.c. guselkumab 100 mg q8w, for 52 weeks, n=42
	guselkumab 200 mg q12w		s.c. guselkumab 200 mg at weeks 0 and 4 then q12w, for 52 weeks, n=42
	adalimumab open-label		s.c. adalimumab dosed according to the labeled dosing for psoriasis for 52 weeks, n=43
endpoints and definitions	primary endpoint	PGA score 0 or 1	number and proportion of randomized subjects with PGA scores of cleared (0) or minimal (1) at week 16
	secondary endpoint	PASI 75	proportion of subjects treated with guselkumab who achieved a PASI 75 response at week 16.
	secondary endpoint	difference between guselkumab and adalimumab in PGA 0/1	the difference of the PGA score of cleared (0) or minimal (1) response rate between guselkumab treatment groups and adalimumab treatment group at weeks 16 and 40.
	secondary endpoint	DLQI	the change in DLQI from baseline at week 16
database lock	the data from this study was to be cleaned and locked for analysis at the week 16, week 40, and week 52 database locks, date study initiated: 25 october 2011, date study completed: 05 august 2013		

Results and analysis								
analysis description	**primary analysis**							
analysis population and time point description	ITT, at week 16							
descriptive statistics and estimate variability	*treatment group*	*adalimumab*	*pbo*	*gus 5 mg q12w*	*gus 15 mg q8w*	*gus 50 mg q12w*	*gus 100 mg q8w*	*gus 200 mg q12w*
	number of subjects	*43*	*42*	*41*	*41*	*42*	*42*	*42*
	PGA 0/1 N, (%)	25 (58.1%)	3 (7.1%)	14 (34.1%)	25 (61.0%)	33 (78.6%)	36 (85.7%)	35 (83.3%)
	PASI 75 *N, (%)*	30 (69.8%)	2 (4.8%)	18 (43.9%)	31 (75.6%)	34 (81.0%)	33 (78.6%)	34 (81.0%)
	DLQI, mean (SD)	-10.1 (9.00)	-2.3 (6.80)	-6.2 (5.24)	-10.3 (5.49)	-11.1 (7.38)	-10.8 (7.34)	-11.4 (6.83)
effect estimate per comparison	primary endpoint: PGA 0/1	comparison groups			adalimumab vs. pbo			
		treatment difference CMH statistics			50.9%			
		(95% CI)			(34.5%, 67.3%)			
		p-value			<0.001			
		comparison groups			guselkumab 5 mg q12w vs. pbo			
		treatment difference CMH statistics			26.9%			
		(95% CI)			(11.0%, 42.7%)			
		p value			0.002			
		comparison groups			guselkumab 15 mg q8w vs. pbo			

		treatment difference CMH statistics	53.8%
		(95% CI)	(37.1%, 70.5%)
		p-value	<0.001
		comparison groups	guselkumab 50 mg q12w vs. pbo
		treatment difference CMH statistics	71.6%
		(95% CI)	(57.2%, 86.1%)
		p-value	<0.001
		comparison groups	guselkumab 100 mg q8w vs. pbo
		treatment difference CMH statistics	78.6%
		(95% CI)	(65.5%, 91.7%)
		p-value	<0.001
		comparison groups	guselkumab 200 mg q12w vs. pbo
		treatment difference CMH statistics	76.2%
		(95% CI)	(62.7%, 89.7%)
		p-value	<0.001
	secondary endpoint: PASI 75	comparison groups	adalimumab vs. pbo
		treatment difference CMH statistics	64.9%
		(95% CI)	(49.9%, 79.9%)
		p-value	<0.001

		comparison groups	guselkumab 5 mg q12w vs. pbo
		treatment difference CMH statistics	39.0%
		(95% CI)	(23.0%, 54.9%)
		p value	<0.001
		comparison groups	guselkumab 15 mg q8w vs. pbo
		treatment difference CMH statistics	70.7%
		(95% CI)	(56.7%, 84.6%)
		p-value	<0.001
		comparison groups	guselkumab 50 mg q12w vs. pbo
		treatment difference CMH statistics	76.2%
		(95% CI)	(62.6%, 89.7%)
		p-value	<0.001
		comparison groups	guselkumab 100 mg q8w vs. pbo
		treatment difference CMH statistics	73.8%
		(95% CI)	(59.8%, 87.8%)
		p-value	<0.001
		comparison groups	guselkumab 200 mg q12w vs. pbo
		treatment difference CMH statistics	76.2%
		(95% CI)	(62.8%, 89.6%)

		p-value	<0.001
	number of subjects with PGA scores of cleared (0) or minimal (1) between guselkumab and adalimumab groups at week 16	comparison groups	guselkumab 5 mg q12w vs. adalimumab
		difference in response rates	-24.0
		95 % CI	(-44.0, -4.0)
		comparison groups	guselkumab 15 mg q8w vs. adalimumab
		difference in response rates	2.8
		95 % CI	(-17.9, 23.5)
		comparison groups	guselkumab 50 mg q12w vs. adalimumab
		difference in response rates	20.4
		95 % CI	(1.5, 39.3)
		comparison groups	guselkumab 100 mg q8w vs. adalimumab
		difference in response rates	27.7
		95 % CI	(9.8, 45.6)
		comparison groups	guselkumab 200 mg q12w vs. adalimumab
		difference in response rates	25.4
		95 % CI	(7.2, 43.6)
	number of subjects with PGA scores of cleared (0) or minimal (1) between guselkumab and	comparison groups	guselkumab 5 mg q12w vs. adalimumab
		difference in response rates	-15.4
		95 % CI	(-37.7, 6.9)
		comparison groups	guselkumab 15 mg q8w vs. adalimumab
		difference in response rates	10.8

	adalimumab groups at week 40	95 % CI	(-10.7, 32.4)
		comparison groups	guselkumab 50 mg q12w vs. adalimumab
		difference in response rates	22.7
		95 % CI	(1.8, 43.6)
		comparison groups	guselkumab 100 mg q8w vs. adalimumab
		difference in response rates	28.7
		95 % CI	(8.5, 49.0)
		comparison groups	guselkumab 200 mg q12w vs. adalimumab
		difference in response rates	32.9
		95 % CI	(13.0, 52.8)

Table 29 - Summary of efficacy for trial PSO3001

TITLE: A Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparatorcontrolled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis (VOYAGE 1)		
Study identifier	**CNTO1959PSO3001**	
Design	Randomized, Double-blind, Placebo and Active Comparator controlled	
	Duration of main phase: Duration of double blind phase Duration of Extension phase:	24 weeks 48 weeks 264 weeks (ongoing)
Hypothesis	Superiority to placebo, noninferiority / superiority to adalimumab	
Treatments	placebo	Placebo for both agents s.c., 16 weeks, N=174

groups	guselkumab		Guselkumab 100 mg q8w s.c., placebo for adalimumab, 160 weeks, N=329
	adalimumab		Adalimumab loading dose 80 mg and 40 mg q2w s.c., placebo for guselkumab, 48 weeks, N=334
Endpoints and definitions	Co-Primary endpoint	PASI 90 and IGA 0/1 at Week 16	Proportion of subjects who achieved IGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (guselkumab vs. Placebo)
	Major Secondary endpoints	IGA 0 w24	Proportion of subjects who achieved IGA 0 at Week 24 (guselkumab vs. adalimumab)
		IGA 0/1 w24	Proportion of subjects who achieved IGA 0/1 at Week 24 (guselkumab vs. adalimumab)
		PASI 90 w24	Proportion of subjects who achieved PASI 90 response at Week 24 (guselkumab vs. adalimumab)
		IGA 0, w48	Proportion of subjects who achieved an IGA score of 0 at Week 48 (guselkumab vs. adalimumab)
		IGA 0/1, w48	Proportion of subjects who achieved an IGA 0/1 at Week 48 (guselkumab vs. adalimumab)
		PASI 90 w48	Proportion of subjects who achieved PASI 90 response at Week 48 (guselkumab vs. adalimumab)
		IGA 0/1, w 16	Proportion of subjects who achieved an IGA 0/1 at Week 16 (guselkumab vs. adalimumab)
		PASI 90 w16	Proportion of subjects who achieved PASI 90 response at Week 16 (guselkumab vs. adalimumab)
		PASI 75 w16	Proportion of subjects who achieved PASI 75 response at Week 16 (guselkumab vs. adalimumab)
		DLQI, w16	Change from baseline in DLQI score at Week 16 (guselkumab vs. placebo)
		ss-IGA 0/1, w16	Proportion of subjects who achieved ss-IGA 0/1 at Week 16 guselkumab vs. placebo)
		PSSD, w16	Change from baseline in PSSD symptom score at Week 16 (guselkumab vs. placebo)
		PSSD symptom score 0, w24	Proportion of subjects who achieved PSSD symptom score of 0 at Week 24 (guselkumab vs. adalimumab)
Database lock	Database locks (DBLs) were planned to occur at Weeks 48 and 160. This CSR represents data from the Week 48 DBL (27 April 2016)		
Results and Analysis			

Analysis description	**Co-Primary Analysis: guselkumab vs. placebo**			
Analysis population and time point description			**ITT, week 16**	
Descriptive statistics and estimate variability	*Treatment group*	*placebo*	*guselkumab*	*adalimumab*
	Number of subject	*174*	*329*	*334*
	IGA score 0/1 N (%)	12 (6.9%)	280 (85.1%)	220 (65.9%)
	PASI 90 responders N (%)	5 (2.9%)	241 (73.3%)	166 (49.7%)

Effect estimate per comparison	IGA 0/1	Comparison groups	guselkumab vs. placebo, week16
		treatment difference CMH statistics	78.1%
		(95% CI)	(73.2%, 83.1%)
		P-value	<0.001
	PASI 90	Comparison groups	guselkumab vs. placebo, week16
		treatment difference CMH statistics	70.4%
		(95% CI)	(65.3%, 75.5%)
		P-value	<0.001

Analysis description	**Secondary analysis: guselkumab vs. adalimumab**		
Descriptive statistics and estimate variability	*Treatment group*	*guselkumab*	*adalimumab*
	Number of subject	*329*	*334*
	IGA score 0, w24 N (%)	173 (52.6%)	98 (29.3%)
	IGA score 0/1, w24 N (%)	277 (84.2%)	206 (61.7%)
	PASI 90, w24 N(%)	264 (80.2%)	177 (53.0%)
	IGA score 0, w48 N (%)	166 (50.5%)	86 (25.7%)

	IGA score 0/1, w48 N (%)	265 (80.5%)	185 (55.4%)
	PASI 90 w48 N(%)	251 (76.3%)	160 (47.9%)
	IGA 0/1, w16	280 (85.1%)	220 (65.9%)
	PASI 90 w16	241 (73.3%)	166 (49.7%)
	PASI 75 w16	300 (91.2%)	244 (73.1%)
	PSSD symptom score 0, w24	90 (36.3%)	59 (21.6%)

Effect estimate per comparison	IGA 0 w24	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	24.5%
		(95% CI)	(17.8%, 31.2%)
		P-value	<0.001
	IGA 0/1, w24	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	23.0%
		(95% CI)	(16.9%, 29.1%)
		P-value	<0.001
	PASI 90, w24	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	27.9%
		(95% CI)	(21.5%, 34.2%)
		P-value	<0.001
	IGA score 0, w48	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	25.6%

		(95% CI)	(19.1%, 32.2%)
		P-value	<0.001
	IGA score 0/1, w48	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	25.4%
		(95% CI)	(18.9%, 31.8%)
		P-value	<0.001
	PASI 90, w48	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	28.8%
		(95% CI)	(22.2%, 35.4%)
		P-value	<0.001
	IGA 0/1, w 16	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	19.3%
		(95% CI)	(13.3%, 25.3%)
		P-value	<0.001
	PASI 90 w16	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	24.1%
		(95% CI)	(17.3%, 30.9%)
		P-value	<0.001
	PASI 75 w16	Comparison groups	guselkumab vs. adalimumab

		treatment difference CMH statistics	18.0%
		(95% CI)	(12.7%, 23.3%)
		P-value	<0.001
	PSSD score 0, w24	Comparison groups	guselkumab vs. adalimumab
		treatment difference CMH statistics	14.8%
		(95% CI)	(7.5%, 22.1%)
		P-value	<0.001

Analysis description	**Secondary analysis: guselkumab vs. placebo**		
Descriptive statistics and estimate variability	*Treatment group*	*guselkumab*	*placebo*
	Number of subject	*329*	*174*
	DLQI, w16, mean	-11.2	-0.6
	SD	(7.24)	(6.36)
	ss-IGA 0/1, w16	231 (83.4%)	21 (14.5%)
	PSSD symptom score, w16, mean	-41.9	-3.0
	SD	(24.61)	(19.56)
Effect estimate per comparison	DLQI, w16	Comparison groups	guselkumab vs. placebo
		LSMean difference (SE) ANOVA	-10.5 (0.68)
		95% CI	(-11.9, -9.2)
		P-value	<0.001
	ss-IGA 0/1, w16	Comparison groups	guselkumab vs. placebo

		treatment difference CMH statistics	69.7%
		95% CI	(63.1%, 76.2%)
		P-value	<0.001
	PSSD, w16	Comparison groups	guselkumab vs. placebo
		LSMean difference (SE) ANOVA	-39.4 (2.69)
		95% CI	(-44.7, -34.1)
		P-value	<0.001
From the secondary and other endpoints only 13 major secondary ones have been included into this table.			

Table 30 - Summary of efficacy for trial PSO3002

TITLE: A Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparator-Controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis with Randomized Withdrawal and Retreatment (VOYAGE 2)			
Study identifier	**CNTO1959PSO3002**		
Design	Duration of active comparator controlled period:		24 weeks
	Duration of randomized-withdrawal period		Week 28-week 72
	Duration of Extension phase:		Week 76-week264 (ongoing)
Hypothesis	Superiority to placebo, noninferiority / superiority to adalimumab		
Treatments groups	placebo	Placebo for both agents s.c., 16 weeks, N=248	
	guselkumab	Guselkumab 100 mg q8w s.c., placebo for adalimumab, 160 weeks, N=496	
	adalimumab	Adalimumab loading dose 80 mg and 40 mg q2w s.c., placebo for guselkumab, 24 weeks, N=248	

Endpoints and definitions	Co-Primary endpoints	PASI 90 and IGA 0/1 at Week 16	Proportion of subjects who achieved IGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16 (guselkumab vs. Placebo)
	Major Secondary endpoints	IGA 0 w24	Proportion of subjects who achieved IGA 0 at Week 24 (guselkumab vs. adalimumab)
		IGA 0/1 w24	Proportion of subjects who achieved IGA 0/1 at Week 24 (guselkumab vs. adalimumab)
		PASI90 w24	Proportion of subjects who achieved PASI 90 response at Week 24 (guselkumab vs. adalimumab)
		loss of PASI 90	Median time to loss of PASI 90 response (guselkumab vs. placebo)
		DLQI, w16	Change from baseline in DLQI score at Week 16 (guselkumab vs. placebo)
		IGA 0/1, w48	Proportion of subjects who achieved an IGA 0/1 at Week 48 (guselkumab vs. adalimumab)
		PASI90 w48	Proportion of subjects who achieved PASI 90 response at Week 48 (guselkumab vs. adalimumab)
		IGA 0/1 w16	Proportion of subjects who achieved IGA 0/1 at Week 16 (guselkumab vs. adalimumab)
		PASI 90 w16	Proportion of subjects who achieved PASI 90 response at Week 16 (guselkumab vs. adalimumab)
		PASI 75 w16	Proportion of subjects who achieved PASI 75 response at Week 16 (guselkumab vs. adalimumab)
		ss-IGA 0/1, w16	Proportion of subjects who achieved ss-IGA 0/1 at Week 16 (guselkumab vs. placebo)
		PSSD, w16	Change from baseline in PSSD symptom score at Week 16 (guselkumab vs. placebo)
		PSSD symptom score of 0, w24	Proportion of subjects who achieved PSSD symptom score of 0 at Week 24 (guselkumab vs. adalimumab)
Database lock	Database locks (DBLs) were planned to occur at Weeks 48 and 160. This CSR represents data from the Week 48 DBL (19 May 2016)		

Results and Analysis				
Analysis description	**Co-Primary Analysis: guselkumab vs. placebo**			
Analysis population and time point description	ITT, week 16			
Descriptive statistics and estimate variability	*Treatment group*	*placebo*	*guselkumab*	*adalimumab*
	Number of subject	*248*	*496*	*248*
	IGA score 0/1 N (%)	21 (8.5%)	417 (84.1%)	168 (67.7%)
	PASI 90 responders N(%)	6 (2.4%)	347 (70.0%)	116 (46.8%)

Effect estimate per comparison	IGA 0/1	Comparison groups	guselkumab vs. placebo, week16
		treatment differences CMH statistics	75.8%
		(95% CI)	(71.3%, 80.2%)
		P-value	<0.001
	PASI 90	Comparison groups	guselkumab vs. placebo, week16
		treatment differences CMH statistics	67.7%
		(95% CI)	(63.5%, 71.8%)
		P-value	<0.001

Analysis description	**Secondary analysis: guselkumab vs. adalimumab**		
Descriptive statistics and estimate variability	*Treatment group*	*guselkumab*	*adalimumab*
	Number of subject	*496*	*248*
	IGA score 0/1, w24 N (%)	414 (83.5%)	161 (64.9%)

	PASI 90 w24 N(%)	373 (75.2%)	136 (54.8%)
	IGA score 0/1, w16 N (%)	417 (84.1%)	168 (67.7%)
	PASI 90 w16 N(%)	347 (70.0%)	116 (46.8%)
	% of patients with PSSD symptom score of 0, w24	144 (35.1%)	45 (22.5%)
	PASI 75, w16	428 (86.3%)	170 (68.5%)
Effect estimate per comparison	IGA 0/1, w24	Comparison groups	guselkumab vs. adalimumab
		treatment differences CMH statistics	18.4%
		(95% CI)	(12.4%, 24.5%)
		P-value	<0.001
	PASI 90, w24	Comparison groups	guselkumab vs. adalimumab
		treatment differences CMH statistics	20.1%
		(95% CI)	(13.5%, 26.8%)
		P-value	<0.001
	IGA score 0/1, w16	Comparison groups	guselkumab vs. adalimumab
		treatment differences CMH statistics	16.4%
		(95% CI)	(10.6%, 22.2%)
		P-value	<0.001
	PASI 90, w16	Comparison groups	guselkumab vs. adalimumab

		treatment differences CMH statistics	23.3%
		(95% CI)	(16.5%, 30.0%)
		P-value	<0.001
	% of patients with PSSD 0, w24	Comparison groups	guselkumab vs. adalimumab
		treatment differences CMH statistics	13.2%
		(95% CI)	(6.3%, 20.1%)
		P-value	<0.001
	PASI 75, w16	Comparison groups	guselkumab vs. adalimumab
		treatment differences CMH statistics	17.7%
		(95% CI)	(11.9%, 23.6%)
		P-value	<0.001
Analysis description	**Secondary analysis: guselkumab vs. placebo**		
Descriptive statistics and estimate variability	*Treatment group*	*guselkumab*	*placebo*
	Number of subject	*496*	*248*
	Time to loss of PASI 90 response (maintenance of response rate (%) at week 48 (20 weeks following randomization), 95% CI	35.4 (28.5, 42.4)	81.8 (75.6, 86.6)
	DLQI, w16, mean	-11.3	-2.6

	SD	(6.82)	(6.85)
	ss-IGA 0/1, w16	329 (80.6%)	22 (10.9%)
	PSSD, w16, mean	-40.4	-8.3
	SD	(26.52)	(23.67)
Effect estimate per comparison	Loss of PASI 90 response	Comparison groups	guselkumab vs. placebo
		maintenance of response rate (%) at week 48 (20 weeks following randomization) (life-table estimate)	46.4%
		95% CI	(37.5%, 55.3%)
		P-value (log-rank)	< 0.001
	DLQI, w16	Comparison groups	guselkumab vs. placebo
		LSMean difference (SE) ANOVA	-8.7 (0.53)
		95% CI	(-9.7, -7.6)
		P-value	<0.001
	ss-IGA 0/1, w16	Comparison groups	guselkumab vs. placebo
		treatment differences CMH statistics	69.5%
		(95% CI)	(64.2%, 74.9%)
		P-value	<0.001
	PSSD, w16	Comparison groups	guselkumab vs. placebo

		LSMean difference (SE) ANOVA	-32.3 (2.17)
		95% CI	(-36.5, -28.0)
		P-value	<0.001
From secondary and other endpoints those 11 have been included into this table.			

Table 31 - Summary of efficacy for trial PSO3003

TITLE: A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Guselkumab for the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis and an Inadequate Response to Ustekinumab			
Study identifier	**CNTO1959PSO3003**		
Design	Randomized, Double-blind, active controlled		
	Duration of open-label phase: Duration of randomised phase: Duration of follow-up phase:		16 weeks 28 weeks (week16-week44) 16 weeks (week44-60)
Hypothesis	Superiority		
Treatments groups	guselkumab		Guselkumab 100 mg q8w s.c., 28 weeks, N=135
	ustekinumab		Ustekinumab 45 mg (>100 kg – 90 mg) at weeks 0 and 4 (and q12 weeks thereafter), N=133
Endpoints and definitions	Primary endpoint	No. of visits with IGA 0/1	Number of visits at which subjects achieved an IGA 0/1 and at least a 2 grade improvement from Week 16 (Week 28 to Week 40)
	Secondary endpoints	No. of visits with PASI 90	The number of visits at which subjects achieved a PASI 90 response (Week 28 to Week 40)
		No. of visits with IGA 0	The number of visits at which subjects achieved an IGA 0 (Week 28 to Week 40)
		IGA 0/1 at week 28	The proportion of subjects who achieved an IGA 0/1 and at least a 2 grade improvement from Week 16 (at Week 28)
Database lock	This study has 2 DBLs, 1 at Week 40 and a final lock when the last subject completes the Week 60 visit. This CSR reports data from the Week 40 DBL.		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT, from week 28 to week 40		
Descriptive statistics and estimate variability	*Treatment group*	*guselkumab*	*ustekinumab*
	Number of subject	*135*	*133*
	No. of visits with IGA 0/1, mean	1.5	0.7
	SD	(1.57)	(1.26)
	No. of visits with PASI 90, mean	2.2	1.1
	SD	(1.69)	(1.53)
	No. of visits with IGA 0, mean SD	0.9 (1.34)	0.4 (1.06)
	IGA 0/1 at week 28, N (%)	42 (31.1%)	19 (14.3%)
Effect estimate per comparison	Primary endpoint No. of visits with IGA 0/1	Comparison groups	Guselkumab vs. ustekinumab
		Difference in Number of visits (SE)	0.8 (0.2)
		95% CI	(0.5;1.2)
		P-value	<0.001
	Secondary endpoint: No. of visits with PASI 90	Comparison groups	Guselkumab vs. ustekinumab
		Difference in Number of visits (SE)	1.1 (0.2)
		95% CI	(0.7;1.5)
		P-value	<0.001

	Secondary endpoint: No. of visits with IGA 0	Comparison groups	Guselkumab vs. ustekinumab
		Difference in Number of visits (SE)	0.6 (0.2)
		95% CI	(0.3;0.9)
		P-value	<0.001
	IGA 0/1 at week 28, N (%)	Comparison groups	Guselkumab vs. ustekinumab
		treatment differences CMH statistics	16.8%
		(95% CI)	(7.1%, 26.6%)
		P-value	<0.001

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

Cross-study comparisons of efficacy focused on the results through Week 24 from the 2 Phase 3 studies (PSO3001 and PSO3002), which included the same subject eligibility criteria, treatment groups, and dose regimens were performed. Study PSO3003 was not included in the cross-study comparisons due to its unique study design, where randomized subjects were those who inadequately responded to ustekinumab.

The comparisons focused on evaluating consistency in guselkumab efficacy across the overall population for:

- The magnitude of treatment effect versus placebo through Week 16 or adalimumab through Week 24
- Time to onset of efficacy and response over time through Week 24
- The above comparisons focused on the measurements common to both studies.

Additionally, the cross-study comparisons also evaluated the consistency in the association of efficacy versus serum guselkumab concentration and efficacy versus antibodies to guselkumab.

Analyses were performed on the pooled data for the same subpopulations that were evaluated in the individual studies for the co-primary endpoints at Week 16, and selected major secondary endpoints at Week 24. For each of the subpopulations, the proportion of subjects achieving a clinical response is presented for the guselkumab and placebo groups (at Week 16) and for the guselkumab and adalimumab groups (at Week 24). Differences in the proportion of subjects achieving a clinical response, and the associated 95% confidence interval (CI) (provided when the number of subjects was at least 10 in each treatment group) for the differences were calculated adjusted by study using Mantel-Haenszel (MH) weights. Formal comparisons were to be performed for subpopulations of

subjects who had a contraindication to, had an inadequate response to, or were intolerant to any of the 3 nonbiologic systemic therapies (PUVA, methotrexate [MTX], or cyclosporine), or for the subpopulations of subjects who had a contraindication to, had an inadequate response to, or were intolerant to etanercept. Nominal p values were provided based on the CMH Chi-square test or Fisher exact text and were only provided if the number of subjects was at least 10 in each treatment group.

Data from studies PSO3001 and PSO3002 were also pooled to assess the association between efficacy and antibody to guselkumab status (see details above, at "ancillary analyses"). Specifically, the proportions of subjects who achieved clinical responses (listed below) at Week 28 were evaluated with respect to the status of antibody to guselkumab (ie, positive or negative) through Week 48.

Psoriasis Improvement

The onset of clinical efficacy as measured by achieving IGA 0/1 and a PASI 90 response occurred as early as Week 2 in both studies (PSO3001 and PSO3002). By Week 8 in both studies, guselkumab treatment responses separated from those of adalimumab. The response separation between guselkumab and adalimumab continued to increase and reached a maximum around Week 16 and 20 for IGA 0/1 and PASI 90 response, respectively, and was maintained through the common Week 24 period.

Figure 18 - IGA 0/1 Over Time (PSO3001 and PSO3002)

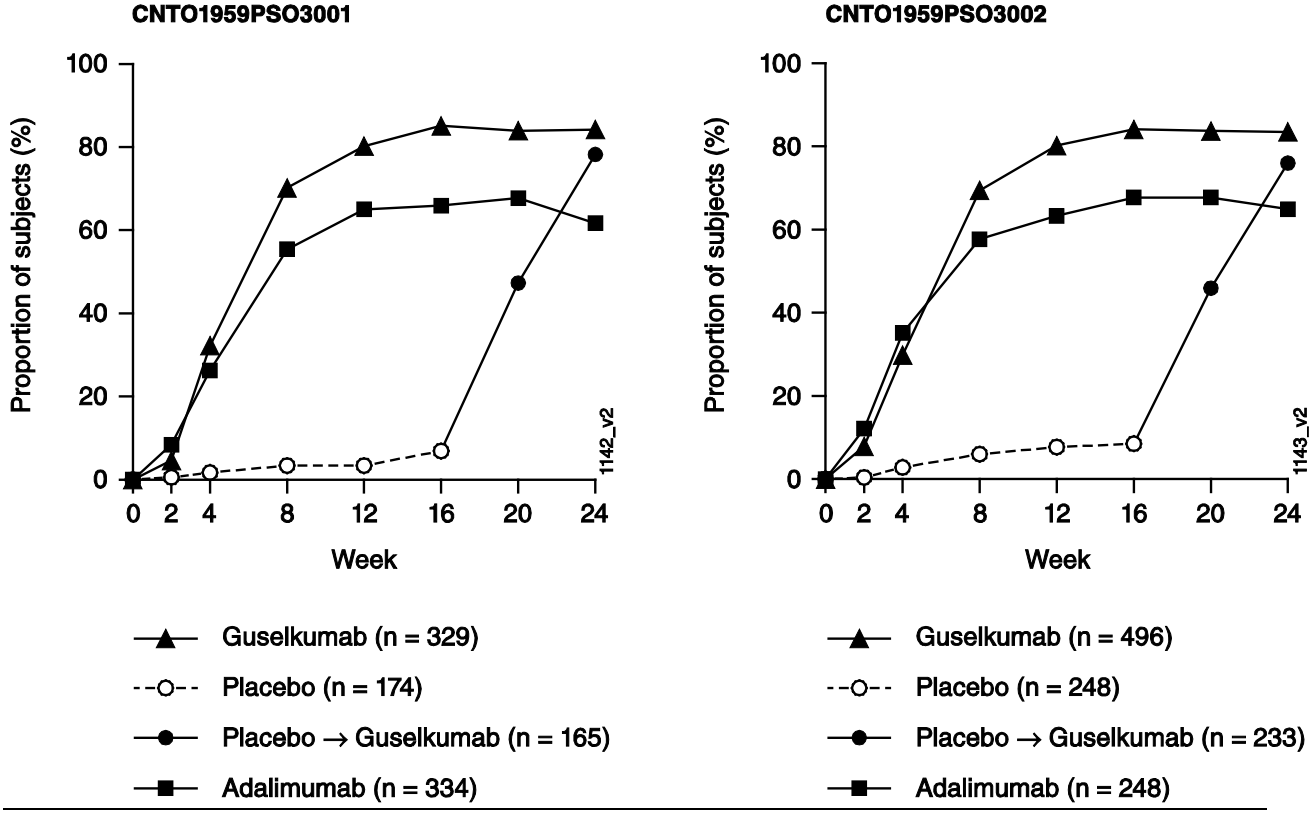
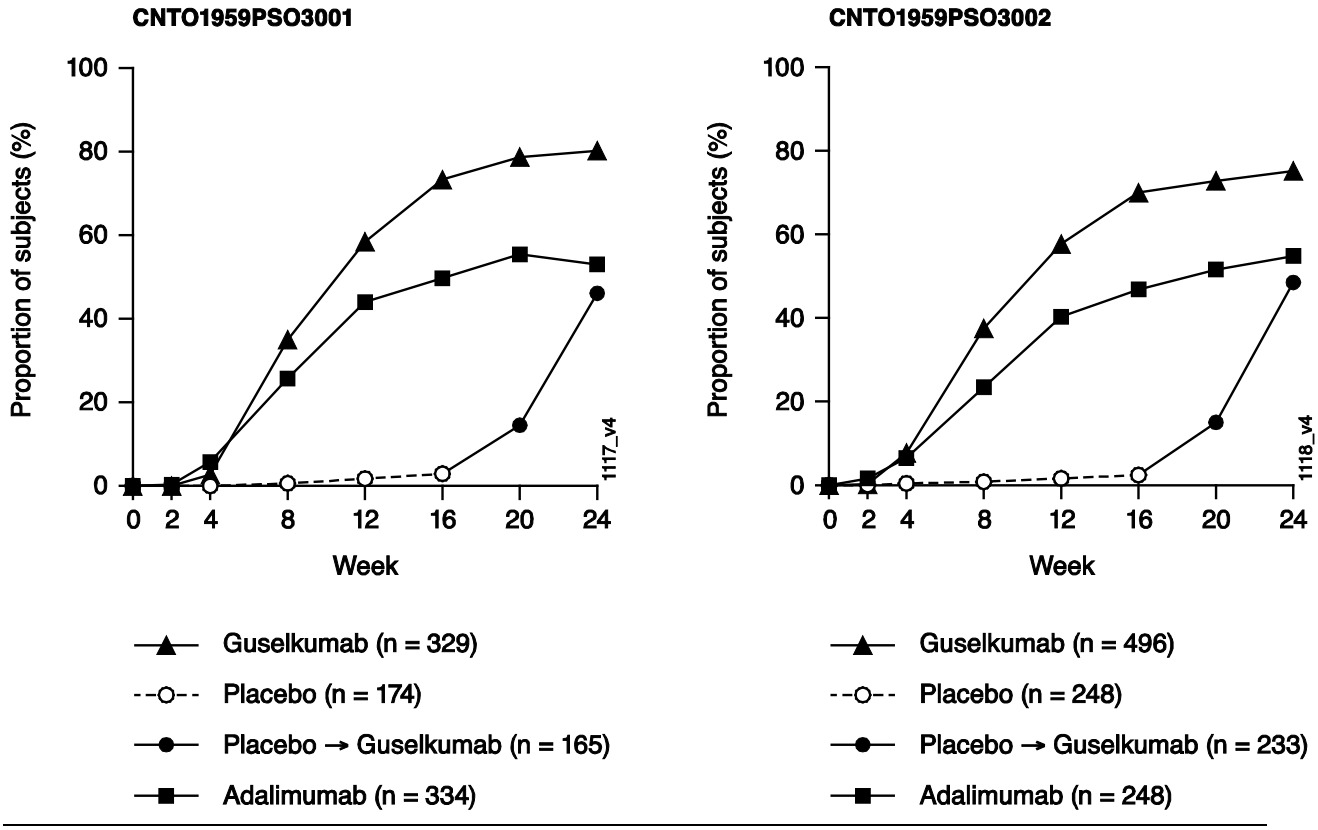


Figure 19 - PASI 90 Response Over Time (PSO3001 and PSO3002)



In the PSO3001 and PSO3002 studies, the response rate as measured by IGA and PASI scores was consistent for each treatment group, and hence, the magnitude of treatment differences in the response rates between treatment groups was consistent between the 2 studies for guselkumab compared with placebo at Week 16, and compared with adalimumab at Week 16 and Week 24

Regional Psoriasis Improvement

Consistent improvements were observed across studies PSO3001 and PSO3002 in scalp psoriasis, nail psoriasis, and hand or foot psoriasis in the guselkumab group compared with the placebo group at Week 16. In addition, in both studies, a significantly higher proportion of guselkumab subjects had scalp psoriasis and hand and foot psoriasis improvement compared with the adalimumab group at both Week 16 and Week 24. Improvement in nail psoriasis was not significantly different between the guselkumab and adalimumab groups in either study as measured by f-PGA or NAPSI at Week 24.

Improvement in Patient-Reported Outcomes

Across both studies (PSO3001 and PSO3002) and consistent with the improvement observed in the physician-assessments (PASI and IGA), significant improvements in patient-reported outcomes of DLQI and PSSD were observed in the guselkumab group compared with the placebo group. Significantly better improvements in patient-reported outcomes of DLQI and PSSD were also observed in the guselkumab group compared with the adalimumab group at Week 24. The magnitude of improvements of these patient-reported outcomes from baseline within treatment groups was consistent between the 2 studies, and treatment differences were also consistent between the 2 studies.

Persistence of Efficacy with Continuous Therapy

Information on the persistence of efficacy during guselkumab treatment is available from both **PSO3001 and PSO3002**. The study PSO3001 evaluated the efficacy of guselkumab compared with adalimumab through Week 48 in the overall population, and therefore provides the best evidence of persistence of efficacy resulting from continuous treatment. Additional information on the persistence of efficacy is also available from analyses of efficacy data from the randomized withdrawal portion of study PSO3002, however, this portion of study PSO3002 was intended to assess the benefit of maintenance therapy versus withdrawal and therefore focused on subjects who were PASI 90 responders at Week 28.

The PSO3001 study results demonstrated that improvement in psoriasis, regional psoriasis, and patient-reported outcomes were all maintained through Week 48 with guselkumab treatment. For example, the proportion of subjects achieving a **PASI 100** response was 37.4% at Week 16, reached a maximum efficacy response of 49.8% by Week 32 and was maintained at **Week 48 (47.4%). PASI 90** response rate was **76.3%** with guselkumab continued treatment at week 48.

In the study PSO3002, persistence of efficacy was observed in PASI 90 responders who continued q8w guselkumab maintenance therapy through Week 48 relative to subjects in whom guselkumab was withdrawn. By life-table estimates, maintenance therapy with guselkumab yielded a significantly higher cumulative PASI 90 response rate compared with withdrawal of therapy through Week 48. Higher response rates were observed with maintenance therapy relative to withdrawal of therapy by a variety of measures including different PASI thresholds (including **PASI 100 responses: 58%** or **PASI 90 responses: 88.6%)** or continuous measures of disease (eg, percentage of PASI improvement from baseline). Through Week 48, other efficacy measures, including measures of nail psoriasis, scalp psoriasis and hand and foot psoriasis also continued to show high response rates, and sustained improvements in patient-reported outcomes were also observed in the maintenance group.

In summary, these results suggest high levels of clinical response and patient-reported outcome response were maintained with continuous guselkumab treatment administered every 8 weeks.

Clinical studies in special populations

Table 3: Number of psoriasis patients ≥65 years in the guselkumab clinical studies

	Age 65-74 (number/total number)	Age 75-84 (number/total number)	Age 85+ (number/total number)
Controlled Trials	89/1748 (5.1%)	4/1748 (0.2%)	0
Non Controlled trials	NA	NA	NA

Supportive studies

Study CNTO1959PSO1001

Study PSO1001 was a randomized, double-blind, placebo-controlled, ascending dose study of guselkumab following a single intravenous (IV) or subcutaneous (SC) administration in healthy subjects (Part 1) and in subjects with **moderate to severe psoriasis** (Part 2).

In Part 2, following a single SC administration of 10, 30, 100 or 300 mg guselkumab to subjects with psoriasis:

- The median percent improvement from baseline in PASI increased across all guselkumab dose groups, with the maximum improvement from baseline observed at Week 12 for the 30 mg (86.60%), 100 mg (75.90%), and 300 mg (98.20%) dose groups and at Week 16 for the 10 mg (76.90%) group
- PGA responses were generally consistent with results of the PASI analysis.

Study CNTO1959PSO1002

Study PSO1002 was a randomized, double-blind, placebo-controlled, ascending single dose study of guselkumab in Japanese subjects with **moderate to severe plaque psoriasis**. The clinical efficacy observed in this study was consistent with Part 2 of study PSO1001.

- The maximum clinical response was observed at Week 16 in all guselkumab dose groups. The median percent improvement from baseline in PASI score at Week 16 in the 10, 30, 100, and 300 mg dose groups (5 subjects each) was 63.16%, 90.95%, 86.67% and 90.65%, respectively, compared to -5.33% in the placebo group (1 subject).

PGA responses were generally consistent with the results of the PASI analysis.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of guselkumab is substantiated by a comprehensive data package including a phase 2 dose-ranging study (PSO2001) and three phase 3 studies (PSO3001, PSO3002 and PSO3003) and some data from phase 1 studies in psoriasis.

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) (further referred as EMA psoriasis guideline). All clinical studies were GCP-compliant and the design of the studies was considered adequate.

Adult subjects were enrolled with moderate to severe plaque psoriasis, defined by a PASI≥ 12, PGA (or IGA)≥ 3, and BSA involvement of at least 10%, who were candidates for systemic or phototherapy. Enrolment criteria were well in accordance with the EMA psoriasis guideline requirements. The patient population of the different studies has been adequately selected.

The primary endpoint was IGA score 0/1 and PASI 90 response in studies PSO3001 and 3002. Choosing the composite endpoint of a global psoriasis assessment tool and PASI response is very well in accordance with the psoriasis guideline requirements. Results obtained with other IL-inhibitors justify the PASI 100/PASI 90 response instead of lowered response rates, however, for comparative purposes, PASI 50 and PASI 75 are also useful parameters. The 5-point IGA 0/1 scores correspond to PASI 90 rather than to PASI 75 response: an improvement of >PASI 90% response and IGA 0/1 both reflect clear or almost clear from psoriatic lesions. The 5-point IGA is a modified version of the 6-point PGA. The 5-point IGA is considered a valid measure of psoriasis disease severity. In line with one of the composite primary endpoints in the other phase 3 studies, non-response to ustekinumab was defined as having IGA>= 2 in study PSO3003. The primary endpoint and several of the major secondary endpoints in study PSO3003 were different from the previous phase 3 studies as it compared the mean number of visits (out of 4 visits between Week 28 and Week 40) with predefined clinical responses (primary endpoint was number of visits achieved an IGA0-1 with at least 2 grade

improvement) between the guselkumab and ustekinumab treatment groups. This approach was utilized primarily to allow for an evaluation of the consistency of response over time and is considered adequate by CHMP. However it did not allow pooling of data with the preceding studies and IGA 0-1 and PASI 90 responses at each visit would have provided this information.

PSSD is a patient-reported outcome measure developed by the Applicant. This was aimed to detect signs and symptoms experienced by a patient on a daily basis. The PSSD has demonstrated strong psychometric properties when validated in a moderate to severe plague psoriasis population. A ≥40-point change from baseline in PSSD symptom score and sign score, and ≥3 to 5 point change in individual PSSD item scale scores were defined as cut-offs for clinical response or clinically meaningful change. The PSSD has 2 versions: a daily diary with a 24-hour recall period and a weekly diary with a 7-day recall period. Both versions were validated, and the validation study showed consistent results between the 2 versions. The daily diary was administered in studies PSO3001 and PSO3002 and the weekly diary was administered in study PSO3003. During validation high internal consistency- and test-retest-reliability were demonstrated. Severity categories by PASI or PGA were well followed by this new instrument, however, sample sizes were sometimes low to draw a firm statistical conclusion. The Applicant elaborated how responder definition (clinically meaningful changes) in PSSD-7d symptom and signs summary score was estimated. It was done by using both an anchor- and distribution-based approach a change of -2 in IGA score and a PASI improvement of ≥ 75 to <90% were considered as reasonable anchors to establish response criteria for the PSSD-7d (Langley et al. 2015; Robinson et al. 2012). Based on the validation report on PSSD, the proposed responder criteria are considered acceptable. PSSD was translated into several languages, too. Based on the evidence submitted in validation report content validity and other measurement properties can be comparable between the original and translated instrument(s).

The Applicant did not seek advice from the EMA regarding the validation of the Psoriasis Symptom and Sign Diary however the Applicant did interact with the FDA and followed for the PSSD development and validation process the FDA's Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009), and was found to be a useful reported outcome tool.

Efficacy data and additional analyses

PSO2001: dose-ranging

A total of 293 subjects were randomized in study PSO2001. The overall completion rate was high (>90%) and discontinuation rates were comparable across arms.

A dose-response relationship was observed in skin-related endpoints such as PASI 50, PASI 75, PASI 90 responder rates, PGA of cleared, PASI score of 0, PGA of cleared or minimal or mild (score 0/1 /2) and quality of life index (DLQI) at week 16. Overall, better results were obtained for the 100 mg s.c. q8w. Dose regimen ≥ 50 mg q12w resulted in better clinical response than adalimumab and all patients in active arms reached higher response than those in placebo. Such a firm dose-response relationship was not apparent at week 40 and 52, however, the 50 mg q12w, 100 mg q8w and 200 mg q12w dose groups performed significantly better than adalimumab and lower guselkumab dose groups. Patients who were switched from placebo to 100 mg q8w guselkumab at week 16 achieved the same magnitude of response than those who were on higher guselkumab doses within 16 weeks of guselkumab treatment.

Based on the outcomes of the phase 2 dose-ranging study it was concluded that 100 mg q8w dose regimen showed overall the best efficacy results which were also the most clinically relevant. Thus, this posology was carried forward in phase 3 studies. To accelerate the onset of effect, a loading dose of 100 mg guselkumab was also given at Week 4 prior to 100 mg q8w maintenance dosing in the Phase 3 program.

The need of an induction dose was thoroughly discussed. The decision on starting with an induction dose was based on PK data and the aim was to increase exposure rapidly. To evaluate whether rapid increase in exposure translate into clinical effect, the Applicant made a cross-study comparison of PASI90 response rates. Response rates of 100 mg q8w/PSO2001 were plotted against response rates of induction dose+100 mg q8w/PSO3001. According to the Applicant, an improvement during the first 20 weeks and a shortening of the time needed to reach the plateau of effect by at least 4 weeks was evident that justify the benefit from the induction dose.

The phase 3 results with the applied dosing regimen demonstrated robust efficacy and safety data, and therefore are acceptable.

When comparing q8w and q12w dosing intervals, a loss of efficacy at the end of dosing interval could be observed for the q12w dosing but not for the q8w dosing group. However, in the phase 3 study (withdrawal phase of study 3002), the proportion of subjects with a PASI 90 response began to decline only 12 weeks after the last dose of guselkumab. Further justification was required by CHMP on the q8w dosing. In study PSO3002, PASI 90 response rate declined 12 weeks after cessation of therapy. This may suggest that longer dosing intervals could have been tested in a larger population. It was considered by the CHMP that the phase 3 studies were performed with the q8w dose regimen and data robustly support high efficacy of guselkumab (with the applied regimen), further analysis is not required for benefit-risk assessment.

In study PSO3002/randomised-withdrawal phase, the placebo groups still had a high% of patients maintaining PASI 50 and 75 responses. The guselkumab maintenance dosage of 100 mg q8w was proposed because it provides optimal efficacy for the majority of patients. The randomized withdrawal results from study PSO3002 demonstrate consistently that a loss of efficacy occurs in some subjects at Week 32, which was the first timepoint at which efficacy was assessed following withdrawal of guselkumab. Although a median time to loss of PASI 90 response of 15.2 weeks for subjects in the withdrawal group likely means that there are some subjects that could maintain efficacy with a lower dosage (longer dose interval or lower dose), efforts to date to prospectively identify a subgroup of subjects (such as demography or psoriasis severity) who could maintain efficacy with lower dosage have not been successful. Thus, the weight of all available evidence, including a favorable safety profile, is consistent with the conclusion that the recommended dose regimen of 100 mg q8w represents the best choice for most patients.

Phase 3 studies

The Phase 3 clinical development program for guselkumab included 2,700 adult subjects (837 in PSO3001, 992 in PSO3002, and 871 in PSO3003). Study population was mainly in line with general psoriasis population in terms of demographics, disease characteristics and medication history and was considered to be adequate. In study 3001, guselkumab treatment arm included smaller proportion of patients with intolerance to/contraindication or inadequate response to at least one biologic therapy (etanercept, ustekinumab, infliximab). This may raise a question whether patients enrolled into guselkumab arm were less treatment resistant, which might influence results. Looking at the totality of data this is, however, very unlikely. Such an imbalance was not observed in study PSO3002 and the results from these two studies (PSO3001 and PSO3002) are highly consistent. The proportion of TNFi

inadequate responders was low in studies PSO3001 and 3002 (c.a.2%). In study 3001, there was a slight imbalance in proportions across arms (placebo, guselkumab, adalimumab, respectively): 10 (5.7%) 7 (2.1%) 5 (1.5%). However, the sample sizes are generally low and results were unlikely biased by this imbalance. Regarding non-biologic systemic medications, 32% of subjects were inadequate responders and distribution across arms was generally similar.

The overall completion rates were high in all three studies (around 90% at week 48 in studies 3001 and 3002). Withdrawals due to non-compliance with study drug were low and comparable across active treatment arms. During the first 16 weeks, discontinuation rate was the lowest in the guselkumab-arm and the highest in the placebo arm. Regarding the reasons of withdrawals, adverse events occurred more frequently in the active arms than in the placebo, while lack of efficacy was the lowest among patients treated with guselkumab. In study PSO3003, the number and rate of discontinuers who stopped treatment due to lack of efficacy were higher in ustekinumab group than in guselkumab group.

Compliance was ensured by utilising electronic tablet device and close site monitoring. The Overall compliance rates were high.

In the phase 3 studies, all protocol amendments occurred before database lock. Protocol violations discussed by the Applicant in the CSRs could not influence the integrity of studies.

Restriction of concomitant psoriasis treatments through only Week 48 was an oversight in the original version of the PSO3002 study protocol. The second amendment of study PSO3002 was issued on 25 June 2015 to restrict the use of concomitant medications for psoriasis through Week 76 instead of through Week 48. The restrictions were extended through Week 76 in order to not confound the efficacy data during the randomized withdrawal portion of the study. At the time of the protocol amendment, no subjects had passed the Week 48 visit, which occurred on 26 October 2015. Therefore, this restricted use of psoriasis concomitant medications should not have had any impact on the study results ITT principles were followed in all three studies.

Outcomes, Studies PSO3001 and PSO3002

The composite primary endpoints of IGA 0/1 and PASI 90 response rate were achieved by significantly higher proportion of subjects with guselkumab than those with placebo in studies PSO3001 and PSO3002 at weeks 16 and 24. These results were confirmed by several sensitivity analyses and per-protocol analysis, too. Adalimumab performed significantly better than placebo.

Secondary endpoints of study 3001 indicate a robust improvement of psoriasis treated with guselkumab: 44%, 80% and 90% of patients were PASI 100, 90 and 75 responders at week 24. 52.6% of subjects were totally cleared as measured by IGA at week 24. All results were almost the same at week 16. In study 3002 highly similar results were obtained at week 24: PASI 100 response: 44% or PASI 90 response: 75%. Guselkumab was superior to placebo and adalimumab in general psoriasis measures (IGA and PASI). Placebo and guselkumab response curves separated from week 2 and adalimumab and guselkumab arms separated from week 8. Clinical response was maintained up to week 48. At week 16 placebo patients were switched to guselkumab and these patients showed the same improvement within 8 weeks (PASI responder rates).

Physician's assessed measures of regional psoriasis in those who had substantial regional manifestations of psoriasis (fingernail-f-PGA, nail-NAPSI, hand-feet- hf-PGA, scalp-ss-IGA) improved significantly more in guselkumab patients than in those subjects who received placebo. A significantly higher proportion of guselkumab subjects had scalp psoriasis and hand and foot psoriasis improvement compared with the adalimumab group at both weeks 16 and 24. Improvement in nail psoriasis was not

significantly different between the guselkumab and adalimumab groups in either study as measured by f-PGA or NAPSI.

All patient-reported outcomes improved better in guselkumab arm than placebo until week 16 and results were significantly better in guselkumab than adalimumab groups. Baseline PSSD scores (defined as the average score of at least 4 days out of the 7 days prior to the Week 0 visit) were missing in 18-22% of subjects in these studies due to initial technical issues with the electronic diary device. These subjects were excluded from PSSD analysis. The Applicant elaborated that key baseline disease characteristics were similar in subjects with PSSD scores and subjects without PSSD scores. In addition, there were no meaningful differences in clinical response as assessed by PASI, IGA, and DLQI at Week 16, Week 24, and Week 48 between subjects with baseline PSSD scores and without baseline PSSD scores. In Study PSO3002, quality of life (DLQI and SF-36) measures indicate that guselkumab patients experienced improvement in their quality of life while placebo-patients did not (improvement in scores was negligible). Anxiety, depression and work limitation in terms of physical and mental demand and performance, decreased significantly more with guselkumab than placebo as rated by patients.

At the end of the randomised-withdrawal period of study PSO3002, a significantly greater proportion of subjects in the guselkumab maintenance group were PASI 90 responders compared with the withdrawal group. Patients randomised to placebo lost efficacy within 15 weeks (median).

As lower or less frequent drug administration to patients whom achieved an acceptable clinical response was not studied it is currently unclear whether patients could maintain their response on lower doses, less frequent administration or indeed have a short break from treatment, however antibody responses would also need to be considered.

Loss of response was apparent from 12 weeks after the last dose of guselkumab and 9 weeks after the last dose of adalimumab. This is not fully in line with the results obtained in the dose-ranging phase 2 study (see above).

Return closer to baseline levels of serum biomarker S100A12 following the last guselkumab dose at Week 40, was mischaracterized as a “rebound” effect. Measured concentrations of this marker are neither indicative nor connected to a clinical psoriasis rebound.

In line with recommendations, relapse was defined as loss of at least 50% of PASI improvement from baseline in patients who achieved a clinically meaningful response and for rebound an event of new erythrodermic or pustular psoriasis, worsening of PASI by 25% or greater from baseline.

Relapse was evaluated in study PSO3002. Only 16 (9%) subjects had relapse during the withdrawal phase. By the fourth week of re-treatment, 69% of re-treated subjects regained PASI50 response. Only one subject experienced rebound of symptoms. Erythrodermic or pustular psoriasis was not observed. Data suggest that rebound following withdrawal of guselkumab-treatment will be extremely rare.

During maintenance of guselkumab treatment, no apparent signs of intolerance could be observed through week 48.

Those who lost clinical response were re-treated with guselkumab in study PSO3002. Due to the small number of evaluable patients and the short duration of the re-treatment period at week 48, no firm conclusion can be drawn regarding a possible decrease/maintenance of effect after re-initiation of guselkumab. Two-thirds of adalimumab nonresponders became PASI 90 responder by week 48 (these adalimumab nonresponders started guselkumab at week 28). Patients treated with guselkumab

achieved significantly higher improvement in all patient reported outcome measures than placebo-patients and attained better results than adalimumab-patients.

Outcomes, Study PSO3003

Enrolled patients received ustekinumab for 16 weeks. PASI response rates were similar to previous Stelara studies (PASI 75 response c.a 70-74%, PASI 90 response c.a. 50%). Inadequate responders to ustekinumab (IGA >=2) were randomised to receive double-blind guselkumab or ustekinumab through week 40 which was the first database lock point for this study. Guselkumab-patients demonstrated significantly better response than those who remained on ustekinumab as measured by the primary endpoint of the number of visits at which subjects achieved an IGA response of cleared (0) or minimal (1) and at least a 2-grade improvement. The results from the primary analysis were confirmed by all sensitivity and per-protocol analyses. The magnitude of effect was highly similar in ustekinumab-inadequate responders (IR) and in adalimumab IRs in Study PSO3002: PASI 90 response rates were achieved with guselkumab treatment by 60% of adalimumab-IRs and also by ustekinumab IRs.

All secondary endpoints supported the primary one. Significantly higher proportions of patients achieved IGA or PASI response rates (at various thresholds) with guselkumab than ustekinumab. Response curves separated from as early as week 4 of randomised treatment. Patients who continued on open-label ustekinumab improved slightly from Week 16 through Week 28, and then were maintained through Week 40, as measured by PASI response rates and IGA score 0. In contrast, the IGA score of cleared (0) or minimal (1) slightly decreased from week 16 through week 40 for these subjects. Similar figures could be observed for subjects randomised to ustekinumab-treatment, from week 32 to week 40 (i.e., IGA 0/1 decreased slightly). Taking into consideration the available data it is considered that a slight decrease in open-label ustekinumab efficacy in study PSO3003 most likely represents variability rather than a real decrease. Regarding decrease in efficacy in subjects randomised to ustekinumab, this can be attributed to the trough timepoint (at the end of q12w dosing). Similar phenomenon was previously described by Leonardi et al. in 2008.

During the randomised period, patient-reported signs and symptoms of psoriasis (PSSD) and quality of life-results (DLQI) supported the outcomes in psoriasis improvement measures.

Although the mechanistic background of superior efficacy of guselkumab to ustekinumab is not fully clear, the Applicant explained that preclinical data suggest that anti-p40 mAbs may be counter-productive in psoriasis disease relief. Ustekinumab binds to the p40 protein subunit that is present in both IL-12 and 23; therefore it blocks both IL-12 and 23-signalling. Guselkumab is more selective: it inhibits only IL-23-signalling by binding to the p19 subunit of IL-23.

The proposal to discontinue treatment in patients who have shown no response after 16 weeks was discussed. In study PSO3001, the proportion of subjects achieving a PASI 100 response was 37.4% at Week 16, reached a maximum efficacy response of 49.8% by Week 32 and was maintained at Week 48 (47.4%). In study PSO3003, among ustekinumab non-responders, some additional improvement could be observed in IGA 0/1 response, and even more apparently in PASI 90 response even after 16 weeks of treatment. These data may suggest that further improvement can be expected beyond week 16 and further clarifications were required from the applicant. The Applicant considered PASI50 response rates as the best surrogate for “no response” and explained that PASI50 responses plateaued at week 16 (5% of subjects in studies PSO3001 and 3002). This approach is considered appropriate by CHMP.

Subgroup analyses

Guselkumab performed significantly better than placebo and in general, was also better than adalimumab regardless of baseline demographic, geographic and disease characteristics.

No rescue therapy for psoriasis was allowed through Week 48 in the Phase 3 studies , however there were some patients whom received steroids for concomitant illness (i.e. not due to psoriasis or psoriatric arthritis). The use of systemic corticosteroids for treatment of psoriasis was not allowed throughout the duration of the Phase 3 studies. The protocols allowed systemic or topical corticosteroid use for indications other than psoriasis, essentially only for AEs, but only in situations where there were no adequate alternatives. Additionally, the protocols stipulated that corticosteroids should be used on a short-term basis, preferably for ≤2 weeks and that longer-term use of corticosteroids may require discontinuation of study drug.

Overall, the use of systemic corticosteroids was low in studies PSO3001 and PSO3002. In study PSO3001, through Week 48, 14 subjects (6 [1.8%] guselkumab-treated, 3 [1.7%] placebo→guselkumab-treated, and 5 [1.5%] adalimumab-treated) received systemic corticosteroids (intravenous or oral) for indications other than psoriasis or psoriatic arthritis. In study PSO3002, through Week 48, 16 subjects (8 [1.6%] guselkumab-treated, 4 [1.6%] placebo→guselkumab-treated, and 4 [1.6%] adalimumab-treated) received systemic corticosteroids (intravenous or oral) for indications other than psoriasis or PsA.

Sensitivity analyses were performed for the co-primary and the major secondary PASI and IGA-related endpoints at Week 24 comparing guselkumab vs adalimumab. In addition, sensitivity analyses in which nonresponder status was assigned to all subjects who received intralesional, topical, or systemic corticosteroids prior to Week 16 for any reason, demonstrated consistent results with the primary analysis.

Clinical response to guselkumab were modestly lower in the >90 kg subgroup compared with the ≤90 kg subgroup in Studies PSO3001 and 3002. The differences in the response rates between the 2 weight subgroups (with a cut-off at 90 kg) seen at week 24 decreased over time and were eventually comparable at Week 48 in the PSO3001 study. It was considered that efficacy superior to placebo was consistently demonstrated across studies and irrespective of subgroups by body weight and consistently across quartiles by steady-state trough concentrations. Efficacy was almost at the plateau of the exposure-response curve. Efficacy responses were high even in those who had steady-state trough serum guselkumab concentrations <0.67 µg/mL at Week 28 (25% of subjects). In study PSO3001, response rates were modestly to slightly lower in the heavier than 90 kg subgroup before Week 24, but comparable at Weeks 24 through Week 48. This was also the case in study PSO3002. The differences in response rates between weight subgroups narrowed with increasing duration of treatment. Analysis of pooled data showed that the placebo response rates were also lower for heavier subjects (>90 kg) compared with lighter subjects (≤ 90 kg). It was hypothesised that intrinsic factors unrelated to guselkumab exposure may have influenced the response rates observed for the two weight strata, however it is agreed that weight dose adjustment is not required.

Unlike the other two phase 3 studies, study PSO3003 was stratified by weight with a cut-off at 100 kg. In this study, better efficacy for guselkumab to ustekinumab in IRs was demonstrated consistently across body weight subgroups (below 100 kg or above 100kg).

Significant treatment by region interaction was found at some endpoints for Study 3001, due to the larger treatment difference in efficacy observed between guselkumab and adalimumab for North American subjects. The Applicant explained the larger treatment differences with the lower efficacy of adalimumab within this subpopulation relative to the non-North American subjects. No significant

treatment by region interaction was found for PSO3002. This is considered only a chance finding without any clinically meaningful relevance.

Guselkumab was significantly more effective than placebo or adalimumab regardless of prior psoriasis therapy, too. The magnitude of effect was similar in subjects previously exposed to biologic therapy and in those who were biologic-naïve. Response rates and treatment effects in the non-biologic IRs were similar to the overall population, for pooled studies. The low number of biologic IRs did not allow robust conclusion on efficacy in these patients.

Supportive data to efficacy were collected in phase 1 psoriasis studies with guselkumab, clinical response (percent improvement in PASI score and PGA response) were high with guselkumab, dose-response could be observed and results were consistent.

The overall incidence of antibody forming to guselkumab after exposure to guselkumab was 5.5% (n=96), titers were generally low. Seven (7.3%) of 96 subjects who were positive for antibodies to guselkumab from the Phase 2 and 3 psoriasis studies had neutralisation antibodies. The overall incidence of neutralizing antibodies to guselkumab in subjects who received guselkumab and had samples that were evaluable for antibodies to guselkumab was 0.4% (7/1,730 subjects) (see safety assessment). Antibody development to guselkumab did not influenced efficacy as measured by IGA and PASI responses at various thresholds. However, the small sample size in these studies limits a definitive conclusion of the impact of antibodies to guselkumab on clinical efficacy. It was however unclear whether prolonged or intermittent therapy could lead to increased antibody formation which could affect safety or efficacy in the longer term.

2.5.4. Conclusions on the clinical efficacy

Guselkumab demonstrated superior efficacy to placebo in all phase 2 and phase 3 clinical studies. The dose carried forward to phase 3 studies is considered generally justified. The magnitude of effect is highly clinically relevant; at week 24 40-45% of subjects were totally cleared from psoriasis. Superiority to an appropriate therapy, a TNF-i adalimumab was also demonstrated. Better efficacy compared to ustekinumab, an IL12-23-inhibitor was also demonstrated in documented ustekinumab inadequate responders. The efficacy of guselkumab was consistent across studies and irrespective of demographic, disease or geographic characteristics or previous psoriasis therapies applied. Primary endpoints were supported by all secondary and other endpoints. From a clinical efficacy perspective, the proposed indication for the treatment of patients with plaque psoriasis requiring systemic therapy can be granted.

2.6. Clinical safety

Patient exposure

Safety data in subjects with moderate to severe plaque psoriasis from two of the global Phase 3 studies (PSO3001 and PSO3002) were pooled, and serve as the primary safety analysis set for the integrated summary analyses of safety. The appropriateness of pooling data from studies PSO3001 and PSO3002 is supported by their shared similarities in study design.

Safety data from the global Phase 3 study PSO3003 and the completed Phase 2 study PSO2001 in plaque psoriasis were not pooled with data from studies PSO3001 and PSO3002 due to the differences in dose regimens (PSO2001) and randomized study populations (PSO3003). Safety data from the

Phase 1 core psoriasis studies, PSO1001 and PSO1002, were not included in the pooled analyses due to the small numbers of subjects and treatment with only a single dose over a wide dose range.

Analyses of adjudicated MACE data were an exception to the pooling strategy described above.

Core Psoriasis Studies

- Guselkumab exposure across the 2 Phase 1 core psoriasis studies (PSO1001 and PSO1002) included the following:

A total of 36 healthy volunteer and 40 subjects with moderate to severe plaque psoriasis received single-dose exposure to guselkumab. Among the 40 subjects with moderate to severe plaque psoriasis treated across these 2 studies, 10 received a single dose of 100 mg SC guselkumab and 10 received a single dose of >100 mg SC guselkumab.

- Guselkumab exposure across the Phase 2 (PSO2001) and Phase 3 (PSO3001, PSO3002, and PSO3003) core psoriasis studies included the following:

Through the end of the reporting period in the combined Phase 2 and Phase 3 core psoriasis studies, 1,748 subjects were treated with guselkumab. This number includes subjects who received treatment with guselkumab only, those who were crossed over from placebo to guselkumab in studies PSO2001, PSO3001, and PSO3002, and those who were crossed over from adalimumab to guselkumab in study PSO3002. Of the total 1,748 guselkumab-treated subjects, 1,393 were exposed for at least 6 months (24 weeks), and 728 were exposed for 1 year (48 weeks). The majority of the guselkumab-treated subjects (90.6%; 1,583 of 1,748) received the 100 mg q8w dose regimen, and 41 subjects (2.3%; all from Phase 2 study PSO2001) received a dose >100 mg (200 mg SC). Across all subjects exposed to guselkumab in the Phase 2 and 3 core psoriasis studies, the average number of administrations was 5.0.

Table 32 – Summary of duration of guselkumab exposure and total guselkumab dose through the end of the reporting period

	Guselkumab at Doses Lower Than 100 mg[a]	Guselkumab 100 mg[b]	Guselkumab 200 mg	All Guselkumab[c]
Analysis set: Subjects treated with guselkumab	124	1583	41	1748
Duration of guselkumab exposure				
At least 6 months[d]	117 (94.4%)	1238 (78.2%)	38 (92.7%)	1393 (79.7%)
At least 1 year[e]	78 (62.9%)	624 (39.4%)	26 (63.4%)	728 (41.6%)

[a] Includes guselkumab 5 mg (q12w), 15 mg (q8w), and 50 mg (q12w) in CNTO1959PSO2001 study.
[b] Includes all subjects treated with guselkumab 100 mg q8w in CNTO1959PSO2001 (including placebo crossover subjects), CNTO1959PSO3001 (including placebo crossover subjects), CNTO1959PSO3002 (including placebo crossover and adalimumab crossover subjects), and CNTO1959PSO3003.
[c] Includes data from Guselkumab at Doses Lower Than 100 mg column, Guselkumab 100 mg column and Guselkumab 200 mg column.
[d] The duration between the first and last guselkumab administration was at least 16 weeks.
[e] The duration between the first and last guselkumab administration was at least 40 weeks.

The number of subjects in the pooled safety analysis set (PSO3001 and PSO3002) who received at least 1 injection of guselkumab through the end of the reporting period was 1,367, with 1,036 subjects

treated for 6 months and 592 subjects treated for 1 year. Across these 2 studies, all guselkumab-treated subjects received the proposed dosage regimen of 100 mg, administered SC, at Weeks 0 and 4 and then q8w thereafter.

Other Clinical Studies

Exposure to guselkumab across the five completed studies in other indications or populations included the following:

A total of 304 subjects were exposed to guselkumab across these studies (149 healthy volunteers, 25 subjects with PPP, 21 subjects with GPP/EP, 109 subjects with RA).

Adverse events

Methods of Safety Analysis

In addition to standard AE analyses, evaluations of events by specific system organ classes (SOC) or syndromes of interest were also performed based on the following:

- mechanistic plausibility in the setting of immunomodulation via cytokine blockade (infections; malignancies);
- identified or potential safety concerns for other anti-cytokine antibody therapies (injection-site reactions [ISR], serious hypersensitivity reactions, and neuropsychiatric events [suicidal ideation and behavior]); or

AEs acknowledged occurring at an increased frequency within the target population of moderate to severe plaque psoriasis (adverse cardiovascular [CV] events, including major adverse cardiovascular events [MACE] and AEs of psoriasis) which could potentially be influenced by cytokine blockade.

Common Adverse Events

Pooled Safety Analysis Set (Core Psoriasis Studies PSO3001 and PSO3002)

Through the Placebo-Controlled Period (Week 16)

The overall proportion of subjects with AEs in the guselkumab group was 49.2% and was comparable with that for the placebo (46.7%) and adalimumab (49.9%) groups.

During the placebo-controlled period, Infections and infestations was the SOC with the highest proportion of AEs in the guselkumab group (22.8%), and the proportion of subjects with AEs in this SOC was generally comparable with that for the placebo (20.6%) and adalimumab (23.6%) groups. For all other SOCs, the proportion of subjects with AEs in the guselkumab group was <10%.

Through the Common Active Comparator-Controlled Period (Week 28)

Data for the placebo/guselkumab group reflect only events after subjects assigned to the placebo group had been crossed over to guselkumab; thus, the average duration of follow-up for the placebo/guselkumab group through Week 28 was shorter than that for the other 2 groups, at approximately 12 weeks (average exposure of 6.8 administrations).

Through Week 28, the overall proportion of subjects with AEs was 60.8% in the guselkumab group and 64.4% in the adalimumab group. The SOC associated with the highest frequency of AEs through Week

28 was Infections and infestations (33.5% and 36.0% in the guselkumab and adalimumab groups, respectively). The most common AEs in this SOC were nasopharyngitis (12.5% and 14.5%, respectively) and URTI (7.4% and 6.0%, respectively). As expected given the shorter exposure and follow-up, the overall frequency of AEs in the placebo/guselkumab group (35.9%) and the frequency of AEs in most SOCs were lower than those for the guselkumab group. The types of reported AEs, however, were similar in the two groups.

Through the End of the Reporting Period (Week 48)

The MedDRA SOC with the highest event rates in the guselkumab group was Infections and Infestations (96.57/100 subj-yrs) followed by General disorders and administration site conditions (22.37/100 subj-yrs) and Skin and subcutaneous tissue disorders (19.19/100 subj-yrs).

In the guselkumab group, the most common AEs through Week 48 were nasopharyngitis (32.84/100 subject-yrs), URTI (17.24/100 subject-yrs), headache (7.29/100 subject-yrs), arthralgia (5.95/100 subject-yrs), and hypertension (5.13/100 subject-yrs). All other AEs in the guselkumab group were reported at rates of <5.0/100 subject-yrs, with most individual AEs reported at rates of <1/100 subject-yrs.

The exposure-adjusted event rate up to week 48 was 259.42/100 subject-yrs in the guselkumab group and 332.84/100 subject-yrs in the adalimumab group.

A comparison of exposure-adjusted rates for AEs in the guselkumab groups across the 3 analysis periods did not show any increase in overall AE event rates over time (330.11, 295.20, and 259.42 per 100 subject-yrs through Week 16, Week 28, and Week 48, respectively.

Event rates for most individual AEs for the guselkumab group were comparable with those for the adalimumab group, with the exception of some ISRs, which were lower for the guselkumab group, specifically, injection site erythema, pruritus, pain and swelling. Also of note, the event rate for the AE of psoriasis was lower in the guselkumab group (1.03/100 subject-yrs vs 4.77/100 subject-yrs in adalimumab group).

Adverse events of special interest

Infections

Although infection is a theoretical risk for guselkumab based on its immune-modulating mechanism of action, the data from the pooled Phase 3 psoriasis studies do not demonstrate a higher rate of infection for subjects treated with guselkumab than for subjects treated with placebo through Week 16 or those treated with adalimumab through the longer analysis periods (Week 28 and Week 48).

- Guselkumab was not associated with an increased frequency of infections requiring the use of oral or parenteral antimicrobial treatment relative to placebo through Week 16.
- The exposure-adjusted rates for infection AEs in the guselkumab groups were stable over the 3 analysis periods, and there was no evidence for an increase in rate with increasing duration of guselkumab exposure.
- With longer treatment (through Week 28 or Week 48), the frequency/rate of infections requiring antimicrobial treatment in the guselkumab group were numerically similar to those for the adalimumab group.

- Through Week 28, nasopharyngitis and URTI continued to be the most common individual infection AEs reported in the guselkumab group (11.5% and 7.4%, respectively), and the frequency of these events was similar to that for the adalimumab group (12.9% and 6.0%, respectively). The 3 serious infections in the guselkumab group through the active comparator-controlled period were bronchitis, soft tissue infection, and erysipelas. Of note, none of the serious infections in the guselkumab group resulted in discontinuation of study drug.
- Common infection AEs through Week 48 in the guselkumab group were nasopharyngitis (30.58/100 subject-yrs), URTI (17.24/100 subject-yrs), and bronchitis (3.39/100 subject-yrs).
- Cellulitis was the only serious infection reported in more than 1 subject in the guselkumab group (rate of 0.21/100 subject-yrs).
- Serious infections occurred infrequently in subjects treated with guselkumab for up to 48 weeks (event rate of 1.03/100 subject-yrs [95% CI: 0.49, 1.89]) as well as in subjects treated with adalimumab (event rate of 1.73/100 subject-yrs [95% CI: 0.75, 3.42]).
- The only specific infection AE that was identified as an ADR for guselkumab was gastroenteritis.
- There was no evidence that the incidence of infections that were serious or required antimicrobial treatment were more frequent in subjects switched from adalimumab to guselkumab therapy compared with subjects who only received active treatment with guselkumab, or that the types of common infection AEs differed for these 2 groups.

Table 33 - Summary of Treatment-Emergent Infections per Hundred Subject-Years of Follow-Up Through the End of the Reporting Period by MedDRA System-Organ Class and Preferred Term; Treated Subjects (Studies CNTO1959PSO3001 and CNTO1959PSO3002)

	Placebo	Guselkumab 100 mg[a]	Adalimumab → Guselkumab 100 mg	All Guselkumab[b]	Adalimumab
Analysis set: Subjects treated	422	1221	146	1367	581
Total subject-years of follow-up	129	974	47	1022	461
Median subject-years of follow-up	0.3	0.9	0.4	0.9	0.9
Any infection event					
Subjects with 1 or more infections	90 (21.3%)	542 (44.4%)	40 (27.4%)	582 (42.6%)	273 (47.0%)
Number of infections per 100 subject-yrs of follow-up	86.17	97.69	112.67	98.38	104.23
Infections requiring antimicrobial treatment					
Subjects with 1 or more infections requiring treatment	30 (7.1%)	199 (16.3%)	6 (4.1%)	205 (15.0%)	95 (16.4%)
Number of infections requiring treatment per 100 subject-yrs of follow-up	26.40	26.48	14.88	25.94	28.17
Serious infections					
Subjects with 1 or more serious infections	1 (0.2%)	9 (0.7%)	0	9 (0.7%)	7 (1.2%)
Number of serious infections per 100 subject-yrs of follow-up (95% CI)[c]	0.78 (0.02, 4.33)	1.03 (0.49, 1.89)	0.00 (0.00, 6.37)	0.98 (0.47, 1.80)	1.73 (0.75, 3.42)

Table 33 - Summary of Treatment-Emergent Infections per Hundred Subject-Years of Follow-Up Through the End of the Reporting Period by MedDRA System-Organ Class and Preferred Term; Treated Subjects (Studies CNTO1959PSO3001 and CNTO1959PSO3002)

	Placebo	Guselkumab 100 mg[a]	Adalimumab → Guselkumab 100 mg	All Guselkumab[b]	Adalimumab

CI=confidence interval; MedDRA= Medical Dictionary for Regulatory Activities; subj-yrs=subject years.
a: Placebo crossover subjects were included in the Guselkumab 100 mg column after crossover to guselkumab.
b: Placebo crossover and adalimumab crossover subjects were included in the All Guselkumab column after crossover to guselkumab.
c: Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.

There were no reports of active TB or an opportunistic infection in any guselkumab-treated subject through Week 48 in studies PSO3001 or PSO3002. Active TB was reported for 2 subjects in the adalimumab group.

Study PSO3003

Among randomized subjects, 31.1% of subjects in the guselkumab group and 22.6% in the ustekinumab group had 1 or more infections; all reported events were nonserious. The proportions of subjects with infections requiring oral or parenteral treatment was generally comparable between the guselkumab subjects (8.1%) and ustekinumab subjects (6.0%).

The Applicant performed the additional analyses, which present infections by treatment group and by type of infection. The most common type of infection was viral, with the most common AEs in this category being nasopharyngitis and URTI. By week 16 viral infections was reported in 16.3% subjects in the guselkumab group as compared to 13.7 % and 16.2% in the placebo and adalimumab group respectively. By week 16 bacterial and fungal infections were reported in 3.2% and 1.7% subjects in the guselkumab group as compared to 3.8% and 0.7% in the placebos group and 5.2% and 0.7% in the adalimumab group respectively. No significant differences between the guselkumab and adalimumab arm were observed by Week 28 and Week 48.

Malignancies

Malignancies were infrequent in the guselkumab group through Week 48, and consisted of 6 reports of NMSC (4 reports of BCC and 2 reports of SCC) and 3 reports of malignancy other than NMSC (the 2 events of prostate cancer reported through Week 28 and an event of invasive papillary breast carcinoma reported after Week 28). In the adalimumab group, there was 1 report of NMSC through Week 48, and no reports of malignancy other than NMSC. The event rates for NMSC through Week 48 were 0.62/100 subject-yrs in the guselkumab group and 0.22/100 subject-yrs in the adalimumab group. Corresponding event rates for malignancies other than NMSC through Week 48 in these 2 treatment groups were 0.31/100 subject-yrs and 0/100 subject-yrs, respectively.

Adjudicated Cardiovascular Events

For the **pooled safety analysis set**, there were no CV events in the placebo group. The event rate for all adjudicated CV events in the guselkumab group was comparable with that for the adalimumab group for all 3 analysis periods.

Through Week 48, the overall rate of adjudicated CV events in the guselkumab group was low (0.82/100 subject-yrs) and not higher than that for the adalimumab group (1.52/100 subject-yrs):

The 4 adjudicated CV events other than MACE reported through Week 48 in the guselkumab group consisted of the 2 reports of hospitalization for unstable angina and the 1 report of heart failure reported during earlier analysis periods, plus 1 event of arrhythmia requiring intervention (sinus node dysfunction) reported between Week 16 and Week 28 in a subject who crossed over from placebo to guselkumab. Two of these 4 subjects had established CV disease and all 4 subjects had a history of at least 2 CV risk factors.

- A total of 4 adjudicated MACE were reported in the guselkumab group (event rate, 0.41/100 subject-yrs). All 4 subjects with MACE had a history of at least 3 CV risk factors.

The event rate for MACE through Week 48 in the guselkumab group was comparable to that for the adalimumab group during this analysis period (n=2; 0.43/100 subject-yrs). Both reports of adjudicated MACE in the adalimumab group were nonfatal MIs that were reported during the placebo-controlled period.

There were no adjudicated MACE in subjects who crossed over from adalimumab to guselkumab.

Results of the sensitivity analysis, integrating adjudicated MACE data from **study PSO2001** with those from the pooled safety analysis set, also revealed a low event rate for MACE through the end of the reporting period (0.58/100 subject-yrs [95% CI: 0.21, 1.25] for the Guselkumab 100 mg group) that was consistent with that based on data from the pooled safety analysis set alone.

In **study PSO3003** in ustekinumab inadequate responders, there were a small number of adjudicated CV events during the randomized treatment period (Week 16 to 40) in the guselkumab (n=4 [3.0%]) and ustekinumab (n=1 [0.8%]) group:

- The 2 adjudicated CV events, other than MACE, reported in randomized subjects in the guselkumab group for study PSO3003 were an arrhythmia requiring intervention (sinus bradycardia) and a hospitalization for unstable angina.
- There was a small number of adjudicated MACE: 2 in the guselkumab group (event rate of 3.25/100 subject-yrs) and 1 in the ustekinumab group (event rate of 1.70/100 subject-yrs). Of note, one of the MACE events in the guselkumab group (MI) occurred in the same subject who had the event of unstable angina.
- The adjudicated CV event rates for study PSO3003 were numerically higher than those based on adjudicated data from the pooled safety analysis set or sensitivity analysis. The confidence intervals for these events rates in PSO3003 were wider than corresponding confidence intervals for analyses involving PSO3001 and PSO3002 or PSO3001, PSO3002, and PSO2001, reflecting the imprecision of the point estimates due to the small number of events and much shorter duration of follow-up for study PSO3003.

Injection-site Reactions

Key findings concerning ISRs in the Phase 3 studies PSO3001 and PSO3002 are as follows:

- The proportion of subjects with ISRs following guselkumab injection through Week 16 or Week 48 was low (2.6%) and lower than the corresponding proportion of subjects reporting ISRs following adalimumab injection for both analysis periods.
- The proportion of guselkumab or adalimumab injections associated with an ISR was 0.7% for guselkumab and 1.3% for adalimumab through Week 48 (rate of placebo injections with ISRs

was 0.3% through Week 48). Of the 50 guselkumab injections associated with ISRs through Week 48, 90% (n=45) were mild, none were considered serious.

- Injection site erythema remained the most common ISR associated with injection of guselkumab (reported in 1.5% of subjects) or adalimumab (reported in 5.3% of subjects) through Week 48.

PSO3003 study

- Injection-site reactions were associated with 1.1% of guselkumab injections, all of which were of mild intensity. The types of ISRs (most common, injection site erythema and injection site swelling) associated with guselkumab injection in this study were similar to those reported in PSO3001 and PSO3002.

Hypersensitivity Reactions

No subject exposed to guselkumab in studies PSO3001, PSO3002 and PSO3003 experienced anaphylactic reactions or serum sickness-like reactions through Week 48.

Cases of angioedema, urticaria and hypersensitivity have been reported in the guselkumab treated subjects. Urticaria was reported more frequently in the guselkumab group as compared to the adalimumab group (1.1% for guselkumab and 0.3% for adalimumab).

Adverse Events of Psoriasis

Adverse events of psoriasis were reported at a low frequency (<1%) in the guselkumab group through Week 16 or Week 48, and the frequency of these events was lower than that reported for the adalimumab group in both analysis periods. No events of erythrodermic or pustular psoriasis were reported in the guselkumab group.

Neuropsychiatric Events

Clinical trial data available with guselkumab as of the cutoff date for this application did not suggest increased risk of SIB events with guselkumab treatment in patients with plaque psoriasis.

Pooled PSO3001/3002 Week 100 data submitted confirmed one completed suicide in study PSO3001 in a guselkumab treated patient with history of depression and restarted SSRI treatment. SIB was reported in five out of 2576 guselkumab treated patients.

Analyses of pooled PSO3001/3002 Week 100 data demonstrate that the rates of investigator-reported SIB remain low (0.19 events per 100 subj-yrs). (In other recent clinical development programs the adjudicated SIB event was 0.06/100 subj-yrs for secukinumab, 0.14/100 subj-yrs for ixekizumab, 0.45/100 subj-yrs for brodalumab and 0.34/100 subj yrs for apremilast.) For ustekinumab the available information is from study 3003 where at Week 40 no SIB events have been reported.

So far no biological mechanism **has been explored** indicating possible association of IL-23 inhibition by guselkumab and SIB.

Other Notable Neurologic Adverse Events

Across the pooled safety analysis set, three neurologic AEs (transverse myelitis, dysesthesia, multiple sclerosis) led to discontinuation of guselkumab treatment, one of which was also considered a SAE.

There were no notable neurologic disorder AEs that were serious or resulted in study drug discontinuation reported in the other Phase 2 or Phase 3 studies in plaque psoriasis (PSO2001 and PSO3003).

Immunogenicity (Antibodies to Guselkumab)

During clinical development, a single validated electrochemiluminescent immunoassay (ECLIA) method incorporating an acid dissociation step to improve detection of anti-guselkumab antibodies in the presence of excess guselkumab using the MSD platform was used to detect antibodies to guselkumab (ie, ADAs) in serum collected from all clinical studies. Serum samples positive for anti-guselkumab antibodies were further characterized in vitro for the neutralization of the biological activity of guselkumab (ie, NAbs to guselkumab). A validated, drug- and IL-23-tolerant competitive ligand binding ECLIA method was used to detect neutralizing antibodies to guselkumab in samples from ADA-positive subjects in the Phase 2 and Phase 3 psoriasis studies. Treatment-emergent ADAs are defined as ADAs that developed post-treatment in patients with negative ADA screens at base.

A total of 1,730 subjects in Phase 2 and 3 psoriasis studies who received guselkumab had post treatment serum samples that were evaluable for antibodies to guselkumab. The overall incidence of antibodies to guselkumab though up to Week 52 after exposure to guselkumab was 5.5% (N=96). Titers of antibodies to guselkumab were generally low with the majority (79.2%) being ≤1:160 up to 52 weeks after exposure to guselkumab.

An additional analysis was performed to determine the incidence of antibodies to guselkumab in subjects who received every scheduled guselkumab administration through Week 44 and had post treatment serum samples that were evaluable for antibodies to guselkumab. Among the 562 subjects in the PSO3001 and PSO3002 studies, the incidence of antibodies to guselkumab was 6.0%, which was consistent with the incidence of ADAs (5.5%) in the overall study population in the Phase 2 and 3 studies.

In each individual Phase 2 and 3 study in subjects with psoriasis (PSO2001, PSO3001, PSO3002, and PSO3003), no apparent impact of antibodies to guselkumab on the PK of guselkumab was observed between subjects who were positive for antibodies to guselkumab and subjects who were negative for antibodies to guselkumab.

In the Phase 2 and Phase 3 studies the development of antibodies to guselkumab and the titer of antibodies to guselkumab were not associated with a reduction in the clinical efficacy of guselkumab.

No impact of antibodies to guselkumab on Injection Site Reactions was observed.

Neutralizing Antibodies to Guselkumab

All 96 subjects who were positive for antibodies to guselkumab from a total of 1,730 subjects in the Phase 2 and 3 studies in subjects with psoriasis (PSO2001, PSO3001, PSO3002, and PSO3003) were evaluable for NAbs to guselkumab. Seven (7.3%) of 96 subjects were positive for NAbs. Therefore, the overall incidence of NAbs in subjects who received guselkumab and had samples that were evaluable for ADAs was 0.4% (7/1,730 subjects).

Serious adverse event / deaths / other significant events

Deaths

As of the 30 June 2016 data cut-off,

- one death was reported in a guselkumab-treated subject across the entire clinical development program, including the core psoriasis Phase 2 and 3 studies, completed studies in healthy volunteers, and completed studies in other indications/populations. This death was due to a myocardial infarction and was reported in a subject with multiple cardiac risk factors in the group that received guselkumab 5 mg every 12 weeks in PSO2001.

After the cutoff date for this submission, the sponsor became aware of 2 additional deaths in ongoing Phase 3 studies and further during the evaluation procedure the Applicant provided information about all six deaths reported in patients receiving guselkumab.

- One death occurred in a guselkumab-treated subject in study PSO3003. This 67 year-old male subject had an SAE of 'carcinoma planoepitheliale of unknown origin' at the time of the final (Week 60) study visit in January 2016.
- In study PSO3001 a 43-year-old male subject with a history of depression died approximately 1 week after his Week 68 visit, as a result of a completed suicide. At screening, the subject was being treated with citalopram (Celexa) for depression. After the Week 60 visit, the subject reported a nonserious AE of depression and citalopram was apparently restarted. The subject had been randomized to the guselkumab treatment group and was participating in the open-label study period.
- One death was reported in study PSO3001 as a result of a brain neoplasm with an onset date on study day 560 in a 65-year-old male subject randomized to guselkumab 100 mg who received his first dose on 16 Apr 2015. His family reported that he experienced the onset of dizziness and became disoriented to time and place. A work-up including a head CT established a diagnosis of brain tumor. The study site was subsequently informed that the subject received only palliative treatment for an astrocytoma, that he developed pneumonia secondary to incapacitation and died.
- One subject, randomized to guselkumab at baseline in study PSO3002, died due to a diabetic coma on study day 623. This subject was a 54-year-old male with a history of diabetes, hypertension and PsA. Other risk factors included obesity. The subject first received study medication on 19 May 2015 and had not reported any AEs throughout the course of the study. At the time of death, the subject was taking glipizide and metformin for treatment of his diabetes, which he began in 2001 and 2008 respectively. He was also taking captopril for high blood pressure and amitriptyline for insomnia, which began prior to study participation. The subject's wife called the investigator to report the death due to a diabetic coma. No autopsy was performed and no other information is available at this time.
- One subject, randomized to adalimumab at baseline and who received guselkumab at Week 28 in study PSO3002, was reported as experiencing "sudden death" on study day 792. This subject was a 44-year-old male with a history of PsA and cardiac arrhythmia. He had been taking bisoprolol since December 2014, 2 weeks before screening. On study day 700 an AE of bradycardia was reported and study agent administration was interrupted. He was treated with sotahexal. The last dose of guselkumab was administered on 08 February 2017 (week 108). An autopsy was performed, but the result has not been released to the subject's wife yet. At this time no other information is available.

- In relation to the case report of this sudden death (Subject CNTO1959PSO3002-20181) the applicant will provide the full autopsy report for review in frame of pharmacovigilance reporting (PSUR).

None of these six deaths seems to be causally associated with guselkumab treatment.

Other Serious Adverse Events

There was no evidence for an increase in the reporting rate for SAEs over time up through Week 48 in subjects treated with guselkumab, and most SAEs reported in subjects exposed to guselkumab were single events.

With longer treatment (through Week 28 or Week 48), the overall frequency and rates of SAEs in the guselkumab group were comparable with those for adalimumab.

In the guselkumab group, the exposure-adjusted rate for SAEs through Week 48 was 6.05/100 subject-yrs and was comparable with that for the adalimumab group.

The SOC associated with the highest frequency of SAEs through Week 48 was Infections and infestations (1.13/100 subject-yrs in guselkumab group; 2.17/100 subject-yrs in adalimumab group).

SAEs in the Cardiac disorders SOC were reported at comparable rates in the guselkumab (0.82/100 subject-yrs) and adalimumab (1.08/100 subject-yrs) groups through the end of the reporting period. SAEs of MI (unadjudicated PTs of myocardial infarction or acute myocardial infarction) were reported for 3 subjects in the guselkumab group and 2 subjects in the adalimumab group.

SAEs of note reported in the guselkumab or adalimumab groups included TB, malignancies, and neuropsychiatric disorders. In addition, a SAE of thrombocytopenia was reported in the guselkumab group; the subject's platelet count decreased to a nadir of 27 kU/L and recovered without intervention after discontinuation of guselkumab (within 8 weeks of last dose).

Laboratory findings

In study PSO3003, the frequencies of CTCAE grade ≥2 abnormalities in hematology and chemistry laboratory values were generally low and comparable between the guselkumab and ustekinumab groups from Week 16 through Week 40.

Hematology

The frequencies of abnormal hematology laboratory values of CTCAE toxicity grade ≥2 in the guselkumab group were low and comparable with those observed in the placebo group (Week 16) or adalimumab group (for each of the 3 analysis periods).

No subject in the guselkumab group had a hematology value of CTCAE toxicity grade 4, and only 2 subjects (0.2%) had a hematology value of CTCAE toxicity grade 3 (both of decreased lymphocytes) **through Week 16.**

No subject in the guselkumab group had a hematology laboratory value of CTCAE toxicity grade 4 **through Week 28**. There were 2 additional reports of CTCAE toxicity grade 3 hematology abnormalities through Week 28 in the guselkumab group (1 report each of decreased platelets and decreased neutrophils).

No subject in the guselkumab group had a hematology laboratory value of CTCAE toxicity grade 4 **through Week 48**. There were no additional reports of CTCAE toxicity grade 3 hematology abnormalities through Week 48 in the guselkumab group. The most common Grade ≥2 hematology abnormality through Week 48 in the guselkumab group was low lymphocyte counts, which occurred in 2.5% of subjects. Most abnormal hematology laboratory results reported through Week 48 were sporadic and eventually improved without alteration or interruption of study drug treatment

Chemistry

For all clinical chemistry parameters evaluated, few subjects in the guselkumab group had a laboratory value of CTCAE toxicity grade ≥2 through Week 16 (≤1.5%), Week 28 (≤2.5%), or Week 48 (≤2.8%).

- The frequencies of chemistry laboratory values of CTCAE toxicity grade 2 or higher in the guselkumab group **through Week 16** were comparable with those for the placebo and adalimumab groups. No subject in any treatment group had a chemistry laboratory value of CTCAE toxicity grade 4 through Week 16. CTCAE toxicity grade 3 chemistry abnormalities were infrequent through Week 16 in all treatment groups; decreased sodium (reported in 5 subjects) and ALT elevations (reported in 2 subjects) were the only CTCAE grade 3 chemistry abnormalities reported in more than 1 subject in the guselkumab group. In all 3 treatment groups, shifts from normal baseline to an elevated value in ALT and AST were the most common clinically relevant shifts and were reported for 7.5% and 5.1% of subjects, respectively, in the guselkumab group; 5.4% and 5.8% of subjects, respectively, in the placebo group; and in 13.1% and 8.6% of subjects, respectively, in the adalimumab group.
- The most common grade ≥2 clinical chemistry abnormalities **through Week 28** in the guselkumab group were elevations in ALT, AST, and total bilirubin elevations, which occurred in 2.5%, 2.3%, and 1.1%, respectively, of subjects in the guselkumab group and 2.3%, 1.7%, and 1.7%, respectively, of subjects in the adalimumab group. There was 1 report of a CTCAE toxicity grade 4 chemistry abnormality through Week 28 (elevated AST), and this occurred in a guselkumab-treated subject in study PSO3001. This abnormality was transient and resolved spontaneously.
- As observed for the Week 28 analysis period, the most common Grade ≥2 clinical chemistry abnormalities **through Week 48** were ALT, AST, and total bilirubin elevations, which occurred in 2.8%, 2.7%, and 1.6% of subjects, respectively, of subjects in the guselkumab group and 4.2%, 1.9%, and 2.1%, respectively, of subjects in the adalimumab group. One additional subject had CTCAE grade 4 clinical chemistry abnormalities (elevations in serum creatinine (1114 µmol/L) and potassium (7.3 µmol/L)) through Week 48. This abnormality occurred in a guselkumab-treated subject in study PSO3001 and resolved spontaneously.

Cases of elevated liver enzymes were reported in subject participating in the studies with guselkumab. The number of cases was small. In addition it is noted that 13 subjects receiving guselkumab who experienced CTCAE grade 3 or 4 liver enzyme abnormalities through Week 48 for studies PSO3001 and PSO3002, 12 subjects had confounding factors.

Electrocardiograms

In study PSO3003, an evaluation of mean changes from baseline in ECG interval values (heart rate, PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval) at Week 16 and Week 40

did not reveal any clinically meaningful changes from baseline in either the guselkumab 100 mg SC or ustekinumab group. Postbaseline ECG abnormalities that were not present at baseline were evident for 2 subjects in the guselkumab group and 5 subjects in the ustekinumab group; the 2 abnormalities in the guselkumab group consisted of first degree atrioventricular (AV) block.

There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (nor in the other core psoriasis studies or the completed studies in other indications or populations). The most common postbaseline abnormalities consisted of conduction abnormalities (mainly first degree AV block) and T-wave abnormalities (mainly flat or inverted wave).

Vital Signs

At Week 16, a high percentage of subjects in PSO3001 and PSO3002 studies had shift from a normal baseline value to an elevated value for diastolic BP and in systolic BP in all treatment groups. For diastolic BP the shift was observed in 23.1%, 19.6%, and 20.1% of subjects in the guselkumab, placebo, and adalimumab groups respectively and for systolic BP, the shift was observed in 33.9%, 35.5%, and 34.8% of subjects in the guselkumab, placebo, and adalimumab groups.

Safety in special populations

Analyses of treatment-emergent AEs, serious AEs, infections and the number of subjects who discontinued due to an AE were performed by the following subgroup: age, gender, race, BMI, weight, baseline disease characteristics, geographic region and by previous use of psoriasis therapies.

The low number of subjects in certain subgroups (eg, subjects ≥65 years) or the overall number of subjects with certain types of events (ie, SAEs, discontinuation due to AEs) may limit the interpretation of the subgroup data.

No studies have been conducted in patients with hepatic or renal impairment.

Age

Overall, fewer than 5% of treated subjects across studies PSO3001 and PSO3002 were 65 years of age or older. The frequency of subjects with 1 or more adverse events, serious adverse events and subjects who discontinued study agent because of adverse events was higher in subjects ≥ 65 years of age in comparison to other age groups.

Table 34 –Summary of key safety events through the end of the reporting period by age group subjects treated with guselkumab

	Guselkumab 100 mg[a]			
	Age (yrs)			
	<65	65-74	75-84	≥85
Analysis set: Subjects treated with guselkumab	1300	65	2	-
Avg duration of follow-up (weeks)	39.01	38.62	36.50	-
Avg exposure (number of administrations)	19.69	19.91	21.00	-
Total AEs	831 (63.9%)	47 (72.3%)	2 (100.0%)	-
Serious AEs - Total	48 (3.7%)	3 (4.6%)	1 (50.0%)	-
Fatal	0	0	0	-
Hospitalization/prolong existing hospitalization	47 (3.6%)	2 (3.1%)	0	-
Life-threatening	3 (0.2%)	1 (1.5%)	0	-
Disability/incapacity	0	1 (1.5%)	0	-
Other (medically significant)	8 (0.6%)	1 (1.5%)	1 (50.0%)	-
AE leading to study agent discontinuation	21 (1.6%)	2 (3.1%)	1 (50.0%)	-
Psychiatric disorders	18 (1.4%)	2 (3.1%)	0	-
Nervous system disorders	112 (8.6%)	6 (9.2%)	0	-
Accidents and injuries	78 (6.0%)	8 (12.3%)	0	-
Cardiac disorders	18 (1.4%)	3 (4.6%)	0	-
Vascular disorders	54 (4.2%)	3 (4.6%)	1 (50.0%)	-
Cerebrovascular disorders[b]	0	0	0	-
Infections and infestations	553 (42.5%)	26 (40.0%)	1 (50.0%)	-
Anticholinergic syndrome	0	0	0	-
Quality of life decreased	0	0	0	-
Sum of postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures	9 (0.7%)	2 (3.1%)	0	-

[a] Placebo crossover and adalimumab crossover subjects were included after crossover to guselkumab
[b] Includes adverse events: MedDRA high level group term (HLGT) of "Central nervous system vascular disorders" under MedDRA system organ class (SOC) of "Nervous system disorders".

Sex

At randomization, approximately 70% of treated subjects in the pooled safety analysis population were men. Up to week 48, the higher frequency of AE/SAEs and infections were observed in women than in men (67.1%; 4.6%; 46.6% for women and 63.2%; 3.4% and 40.9% for men respectively). This pattern was also generally apparent for the placebo group through Week 16 and for the adalimumab group through Week 16, 28, or 48.

Race

At randomization, approximately 82% of subjects in the pooled safety analysis set were white and approximately 14% were Asian; thus interpretation of data regarding the impact of race upon safety is limited due to the small number of subjects in the other racial subgroups. Of note, both Investigator's Global Assessment (IGA) 0/1 and PASI 90 were positive for 2 non-white subpopulations (Asian and Black/African American) which shows that guselkumab treatment is effective in these populations as well.

BMI, Weight

The mean BMI at baseline for subjects in the pooled safety analysis set was ~29 and approximately 58% of subjects weighed ≤90 kg and approximately 42% weighed >90 kg across the three treatment groups. No trends were observed with regard to differences in the proportions of subjects with AEs, SAEs, infections, or who discontinued due to an AE as a function of baseline BMI or weight for any of the 3 analysis periods. In addition, there was no evidence that comparisons of the safety profile for the

guselkumab group with the placebo group (Week 16) or adalimumab groups (Weeks 16, 28, or 48) differed as a function of baseline BMI or weight.

Baseline Disease Characteristics, Previous Use of Psoriasis Therapies

Higher reporting rates for AEs and infections among subjects who had ever had prior treatment with phototherapy compared with those who had never received such therapy were reported in the guselkumab group (e.g phototherapy used in the past: AE 68.1%, infections 47.8%; phototherapy never used in the past AE 59.7%, infections 36.0%). This trend was also observed in other treatment groups. No other consistent trend was apparent across the analysis periods in the reporting rates for AEs, infections, SAEs, or AEs leading to discontinuation as a function of prior use of nonbiologic or biologic psoriasis medications or disease characteristics (PASI, IGA, BSA) for the guselkumab group.

Safety related to drug-drug interactions and other interactions

An *in vitro* study using human hepatocytes showed that IL-23 at levels of 10 ng/mL did not alter human CYP enzyme expression or activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). These results suggest that the likelihood of therapeutic proteins-drug interactions between guselkumab and CYP substrates is low.

A phase 1, Open-label, Drug Interaction Study to Evaluate the Effect of Guselkumab (CNTO 1959) on Cytochrome P450 (CYP) Enzyme Activities Following a Single Subcutaneous Administration in Subjects with Moderate to Severe Plaque-type Psoriasis" was completed during the evaluation procedure.

The results from the *in vivo* study indicate that systemic exposures of midazolam, S-warfarin, omeprazole, dextromethophan and caffeine (probe substrates of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2, respectively) were not affected by treatment with guselkumab indicating interactions between guselkumab and CYP substrates (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely in subjects with psoriasis. These results are reflected in the SmPC Section 4.5 'Interaction with other medicinal products and other forms of interaction'.

Discontinuation due to adverse events

Study PSO3001 and Study PSO3002

Discontinuation of treatment with guselkumab 100 mg SC for an AE(s) was infrequent in PSO3001 and PSO3002, and the frequency of discontinuation of study drug due to AEs was similar for the guselkumab and placebo groups through Week 16.

There was no evidence for an increase in the event rate of AEs leading to discontinuation of guselkumab therapy over time. Additionally, most AEs leading to discontinuation of guselkumab treatment were single events.

The overall frequency and rates of AEs leading to discontinuation were no higher for the guselkumab group than for the adalimumab group for the Week 28 and Week 48 analysis periods.

In the guselkumab group, all individual AEs that resulted in discontinuation of study drug through Week 48 were reported at very low rates of ≤0.2/100 subject-yrs, representing 2 or fewer subjects experiencing the event through the entire reporting period.

A comparison of event rates for AEs leading to discontinuation for the guselkumab groups across the 3 analysis periods did not show any increase in rates for early treatment withdrawal over time (4.31, 3.88, and 2.36 per 100 subject-yrs through Week 16, Week 28, and Week 48, respectively).

Study PSO3003

The proportions of subjects who discontinued study drug due to 1 or more treatment-emergent AEs were 2.2% for subjects treated with guselkumab and 1.5% for subjects treated with ustekinumab.

Post marketing experience

Guselkumab has not been marketed in any country.

2.6.1. Discussion on clinical safety

Short term risks

A total of 1,748 subjects with moderate to severe plaque psoriasis were exposed to guselkumab across the Phase 2 and Phase 3 core psoriasis studies (PSO2001, PSO3001, PSO3002, and PSO3003), 728 of whom were exposed to guselkumab for 1 year. A considerable number of patients have been exposed to guselkumab at the recommended dosage and the safety database is considered sufficient.

The adverse event (AE) profile for guselkumab was generally comparable with placebo through Week 16. The most common AE in all treatment groups was nasopharyngitis. There was no increase in the event rate for AEs with longer exposure to guselkumab, and the types of events reported were similar across the three analysis periods. The proportion of subjects reporting one or more AEs for guselkumab through Week 28, as well as the overall AE event rate through Week 48, was not higher than for adalimumab. In general, the rates for AEs within each SOC through Week 28 and 48 were similar for the guselkumab and adalimumab groups, with the exception of some ISRs like injection site erythema, pruritus, pain and swelling, which were lower for the guselkumab group. The SOC associated with the highest frequency of AEs across the three analysis periods was Infections and infestations, the most common AEs through Week 48 in the guselkumab group were nasopharyngitis (32.84/100 subject-yrs), URTI (17.24/100 subject-yrs), headache (7.29/100 subject-yrs), arthralgia (5.95/100 subject-yrs), and hypertension (5.13/100 subject-yrs).

The frequency of discontinuation of study drug due to AEs was similar for the guselkumab and placebo groups through Week 16. The overall frequency and rates of AEs leading to discontinuation were lower for the guselkumab group than for the adalimumab group for the Week 28 and Week 48 analysis periods. A comparison of event rates for AEs leading to discontinuation for the guselkumab groups across the three analysis periods did not show any increase in rates for early treatment withdrawal over time. In the guselkumab group, the Nervous system disorder SOC was associated with the highest number of subjects discontinued for AEs through Week 16 (n=3, 0.4%). Prostate cancer was the only individual AE that resulted in study drug discontinuation in more than one subject in the guselkumab group (n=2) through week 28. One subject was discontinued due to SCC of the skin. Most AEs leading to discontinuation of guselkumab treatment were single events.

Potential long term risks

There was no increase in the event rate for AEs with up to 48 weeks exposure to guselkumab, and the types of events reported were similar across the three analysis periods. Long term safety has been included in the RMP as missing information.

Six deaths were reported from clinical trials in patients with plaque psoriasis receiving guselkumab. None of them seems to be associated with guselkumab therapy.

The proportion of subjects with serious adverse events was low in the guselkumab group and similar to that for the placebo group through Week 16. The overall event rate for SAEs in the guselkumab group was stable across the three analysis periods. The most common SAEs in guselkumab-treated subjects were infection-related events. The proportion of subjects with one or more SAEs through Week 28, as well as the event rate for SAEs through Week 48, in the guselkumab group was comparable with those for the adalimumab group.

Adverse events of special interests evaluated were infections, malignancies, cardiovascular events, injection site and immune reactions, adverse events of psoriasis and neuropsychiatric events.

Infections

Although infection is a theoretical risk for guselkumab based on its immune-modulating mechanism of action, data from the pooled safety analysis set did not demonstrate a higher rate of infection for subjects treated with guselkumab compared with subjects treated with placebo through Week 16 or compared with those treated with adalimumab through the longer analysis periods (Week 28 and Week 48). These infections were generally mild to moderate in severity, responsive to treatment and did not require treatment discontinuation. Nasopharyngitis, URTI and bronchitis were the most common individual infection AEs reported in the guselkumab group, and the frequency of these events was similar to that for the adalimumab group. The overall event rate for infection AEs did not appear to increase over time in subjects receiving active treatment with guselkumab, and were 97.90, 91.32, and 97.69 per 100 subject-yrs through Week 16, Week 28, and Week 48, respectively.

Serious infections with guselkumab were infrequent, with most being single events without a clear pattern. Regarding tuberculosis, subjects with latent TB based on a newly identified positive TB test during screening were eligible to participate in the study if active TB was ruled out and appropriate treatment for latent TB was initiated before or simultaneously with the first administration of guselkumab. A small percentage of subjects in studies PSO3001 (5.9%) and PSO3002 (8.1%) received concomitant treatment for latent TB during the study. No events of tuberculosis or opportunistic infection were reported in guselkumab-treated subjects. Although the lack of latent TB reactivation is reassuring, since only subjects with newly identified positive TB test were eligible for study participation who were also concomitantly receiving antituberculosis therapy the amount of information on the effect of IL23 depletion on possible TB reactivation/antituberculotic immune defense is considered scarce. The event rate for serious infections through Week 48 was 1.03/100 subject-yrs (95% confidence interval: 0.49, 1.89) in the guselkumab group and 1.73/100 subject-yrs (95% CI: 0.75, 3.42) in the adalimumab group.

Cellulitis was the only serious infection reported in more than 1 subject in the guselkumab group (rate of 0.21/100 subject-yrs).

Additional analyses were performed, which present infections by treatment group and by type of infection. The most common type of infection was viral, with the most common AEs in this category being nasopharyngitis and URTI. By week 16 viral infections was reported in 16.3% subjects in the guselkumab group as compared to 13.7 % and 16.2% in the placebo and adalimumab group respectively. By week 16 bacterial and fungal infections were reported in 3.2% and 1.7% subjects in the guselkumab group as compared to 3.8% and 0.7% in the placebos group and 5.2% and 0.7% in the adalimumab group respectively. No significant differences between the guselkumab and adalimumab arm were observed by Week 28 and Week 48.

Based on the biological target and previous experiences with immune-modulating biological medicinal products in real life, serious infections are addressed as an important potential risk in the RMP.

Malignancies

Malignancies among subjects treated with guselkumab were reported infrequently through Week 48 in the pooled safety analysis set, and consisted of six reports of nonmelanoma skin cancers (NMSC) and three reports of other malignancies (prostate cancer and invasive papillary breast carcinoma).

The event rate for NMSC through Week 48 was 0.62/100 subject-yrs in the guselkumab group and 0.22/100 subject-yrs in the adalimumab group. Corresponding event rates for malignancies other than NMSC through Week 48 in the guselkumab and adalimumab groups were 0.31/100 subject-yrs and 0/100 subject-yrs, respectively.

During the evaluation procedure, the Applicant provided follow up results regarding malignancies and a discussion on the background rates of malignancies among psoriasis patients, particularly for non-melanoma skin cancer (NMSC) and melanoma. Data demonstrates that malignancies continue to occur infrequently among guselkumab-treated subjects, and the higher event rate of malignancies reported for the guselkumab group in comparison to the adalimumab group noted through the end of the reporting period in the original MAA submission is no longer evident with longer term follow up.

During the evaluation procedure, the Applicant completed Week 100 database locks for both the PSO3001 and PSO3002 studies with 723 subjects with at least 2 years of exposure to guselkumab. This exposure is still considered short to draw any final conclusions as to the etiology of the observed malignant diseases.

The malignancy rates based on these pooled Week 100 data are consistent with those at the time of the initial submission, and are similar to those reported in the literature among patients with plaque psoriasis and with that observed for other treatments in patients with psoriasis.

Considering the theoretical risk of malignancy associated with all immunomodulating agents, including guselkumab, malignancies are considered as an important potential risk in the risk management plan. The Applicant has committed to monitor the risk of malignancy through additional pharmacovigilance activities and will re-evaluate the need for updating Section 4.4 of SmPC Warnings and Precautions as more safety information becomes available.

Cardiovascular Events

For the pooled safety analysis set, the event rate for adjudicated MACE in the guselkumab group was comparable with that for the adalimumab group through Week 28 and Week 48. In the Phase 3 study in ustekinumab inadequate responders (PSO3003), adjudicated MACE occurred in 2 subjects in the guselkumab group (1.5%) and 1 subject in the ustekinumab group (0.8%), thus event rate (3.25/100 subject-yrs) was significantly higher than in other studies during the randomized treatment period (Week 16 to 40).

It was further clarified that concerning MACE rate in study PSO3003 due to the small number of guselkumab treated subjects and shorter duration of follow-up, data are imprecise and a better estimate of MACE rates for guselkumab can be derived from the pooled data for studies PSO3001 and PSO3002.

CHMP considered that there is currently no evidence for any increase in MACE events in adult patients with plaque psoriasis.

Injection-site and Hypersensitivity Reactions

ISR were reported in a higher incidence in patients treated with guselkumab than in the placebo group, but lower than following adalimumab injection. Injection site erythema remained the most common ISR associated with injection of guselkumab (reported in 1.5% of subjects) or adalimumab (reported in 5.3% of subjects) through Week 48. Most injection site reactions were mild in severity and did not lead to treatment discontinuation.

No cases of anaphylactic reaction or serum sickness like reaction were reported among guselkumab-treated subjects in either the pooled safety analysis set or in the other core Phase 2 or 3 psoriasis studies (PSO2001, PSO3003). Nevertheless serious hypersensitivity is mentioned in the RMP as important potential risk, as this could potentially be expected with this biological product.

No association between injection site reactions and treatment-emergent anti-drug antibodies was established.

Information on serious hypersensitivity reactions are addressed in 4.4 of SmPC.

Cases of angioedema, urticaria and hypersensitivity have been reported in the guselkumab treated subjects. Urticaria was reported more frequently in the guselkumab group as compared to the adalimumab group (1.1% for guselkumab and 0.3% for adalimumab).

Adverse Events of Psoriasis

Adverse events of psoriasis were reported at a low frequency (<1%) in the guselkumab group through Week 16 or Week 48, and the frequency of these events was lower than that reported for the adalimumab group in both analysis periods. No events of erythrodermic or pustular psoriasis were reported in the guselkumab group.

Neuropsychiatric Events

There are data suggesting that depressive symptoms and suicidal ideation are more frequent among patients with psoriasis than in the general population although no firm connection has been established so far. Across all completed or ongoing Phase 1, Phase 2, or Phase 3 studies in plaque psoriasis or other indications, one event of completed suicide (the patient had a history of depression and suicidal ideation), four events of suicidal ideation and one case of suicidal behaviour was reported in guselkumab-treated subjects based on submitted pooled PSO3001/3002 Week 100 data.

Incidence rates of adjudicated suicidal ideation and behavior (SIB) events based on the Columbia Classification Algorithm of Suicide Assessment for the pooled safety analysis set were 0.10 (0.00, 0.57) and 0.43 (0.05, 1.57) per 100 subject-yrs in the guselkumab and adalimumab groups, respectively, through Week 48. These rates were based on a single nonserious AE of suicidal ideation in a guselkumab-treated subject and two SAEs of suicide attempt in adalimumab-treated subjects. The guselkumab-treated subject had a history of depression and suicidal ideation.

Analysis of pooled PSO3001/3002 Week 100 data for guselkumab demonstrate that the rates of investigator-reported SIB is low (0.19 events per 100 subj-yrs), is similar to ixekizumab (0.14/100 subj-yrs), is above of secukinumab (0.06/100 subj-yrs) and appears to be more favorable than that for brodalumab (0.45/100 subj-yrs) and for apremilast (0.34/100 subj yrs).

Although it is agreed that a causal association between treatment with guselkumab and an increased risk of suicidal ideation and behaviour has not been established, continuous monitoring for such events through routine pharmacovigilance, and periodical re-evaluation of emerging data is strongly supported.

Laboratory Findings

The frequencies of abnormal hematology laboratory values of CTCAE toxicity grade ≥2 in the guselkumab group were low (through Week 16 (≤1.5%), Week 28 (<2.0%), and Week 48 (≤2.6%)) and comparable with those observed in the placebo group (Week 16) or adalimumab group (for each of the three analysis periods).

Additional data concerning the potential relationship between systemic blockade of IL-23 and decreases in neutrophil and platelet counts was provided. This data demonstrated decreases in both neutrophil and platelet counts greater on guselkumab treatment than on placebo, but less than observed for adalimumab. These decreases were mostly small (within the normal range) and of no clinical relevance.

There were no CTCAE Grade 4 decreases in neutrophil or platelet counts and there was a single Grade 3 decrease in neutrophil counts and a single Grade 3 decrease in platelet counts among all guselkumab-treated subjects.

There was no unique time course observed for the onset of these abnormalities in the guselkumab group and there was no clear evidence that the occurrence of the neutrophil abnormalities resulted in an increased frequency of infections.

For all clinical chemistry parameters evaluated, few subjects in the guselkumab group had a laboratory value of CTCAE toxicity grade ≥2 through Week 16 (≤1.5%), Week 28 (≤2.5%), or Week 48 (≤2.8%). The most common Grade ≥2 clinical chemistry abnormalities were ALT, AST, and total bilirubin elevations.

No trends were observed that suggested any association between guselkumab and changes in routine laboratory parameters.

Cases of elevated liver enzymes were reported in subject participating in the studies with guselkumab. The number of cases was small. In addition it is noted that 13 subjects receiving guselkumab who experienced CTCAE grade 3 or 4 liver enzyme abnormalities through Week 48 for studies PSO3001 and PSO3002, 12 subjects had confounding factors.

Based on the currently available data a causal association between treatment with guselkumab and increased liver enzymes has not been established. In addition, in general serious drug-induced hepatotoxicity is rare with existing biologic agents although the risk exists.

Liver function tests will continue to be monitored in the clinical trial and postmarketing setting.

There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (nor in the other core psoriasis studies or the completed studies in other indications or populations).

At Week 16, a high percentage of subjects in PSO3001 and PSO3002 studies had shift from a normal baseline value to an elevated value for diastolic BP and in systolic BP in all treatment groups. There is no obvious explanation for the observed shifts from normal to elevated blood pressure. As these changes were observed in a comparable proportion of subjects in all treatment groups suggest it is unlikely that these findings are attributable to exposure to guselkumab. Blood pressure is routinely assessed in clinical trials with guselkumab and hypertension will be added as a specific safety topic in PSURs.

Subpopulations

Overall, no trends were apparent with regard to differences between the guselkumab and placebo groups (through Week 16) or guselkumab and adalimumab groups (through Week 16, Week 28, or Week 48) in the proportions of subjects with AEs, SAEs, infections, or who discontinued due to AEs, when evaluated by demographics, baseline disease characteristics, prior medications or therapies for psoriasis, or geographic region. The low number of subjects in certain subgroups (eg, subjects ≥65 years, 70% of treated subjects were men, 82% of subjects were white) or the overall number of subjects with certain types of events (ie, SAEs, discontinuation due to AEs) may limit the interpretation of the subgroup data.

The frequency of subjects with 1 or more adverse events, serious adverse events and subjects who discontinued study agent because of adverse events was higher in subjects ≥ 65 years of age in comparison to other age groups. However as the number of subjects exposed was small, final conclusion in relation to this issue cannot be made. In addition the same trend was observed in other treatment groups.

Use in patients ≥ 65 years of age has been included in the RMP as missing information in the safety specification. Analysis of use in patients ≥ 65 years of age will be provided in the PBRER/PSUR. No additional pharmacovigilance activities are deemed necessary. A statement addressing the limited experience with guselkumab in patients ≥65 years of age has been included in the SmPC section 4.2 accordingly.

At randomization, approximately 70% of treated subjects in the pooled safety analysis population were men. Up to week 48, the higher frequency of AE/SAEs and infections were observed in women than in men (67.1%; 4.6%; 46.6% for women and 63.2%; 3.4% and 40.9% for men respectively). This pattern was also generally apparent for the placebo group through Week 16 and for the adalimumab group through Week 16, 28, or 48.

Higher reporting rates for AEs and infections among subjects who had ever had prior treatment with phototherapy compared with those who had never received such therapy were reported in the guselkumab group (e.g phototherapy used in the past: AE 68.1%, infections 47.8%; phototherapy never used in the past AE 59.7%, infections 36.0%). This trend was also observed in other treatment groups

Information on long term safety and the treatment of certain subpopulations of patients, as treatment of pediatric patients, patients with severe hepatic and renal impairment, pregnant and breastfeeding patients, treatment of the very elderly is missing and is mentioned as missing information in the RMP.

Immunological events

Approximately 5.5 % of patients treated with guselkumab at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titers and not associated with reduced clinical response up to 48 weeks of treatment. Approximately 0.4 % of patients treated with guselkumab had confirmed neutralizing antibodies. An association between immunogenicity and treatment emergent adverse events has not been established.

2.6.2. Conclusions on the clinical safety

Although the overall adverse event rates of guselkumab in the pooled data and for Study PSO3003 are considered to be similar to the active comparator adalimumab and ustekinumab respectively, the safety profile of guselkumab seems to be considerably more favorable than that of the TNF inhibitor

treatments especially in terms of serious infections, hypersensitive reactions, autoimmune diseases, nervous system and cardiac disorders.

The long term safety of guselkumab was evaluated following 48 week treatment at submission, and since then the Applicant has completed Week 100 database locks for both the PSO3001 and PSO3002 studies with 723 subjects with at least 2 years of exposure to guselkumab. However, considering the length of tumor induction still no conclusions concerning the possible etiology/causality of the observed malignant diseases can be made.

One event of completed suicide, four events of suicidal ideation and one case of suicidal behaviour was reported in guselkumab-treated subjects as of Week100; this will be monitored in the post marketing phase.

Approximately 5.5 % of patients treated with guselkumab at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titers and not associated with reduced clinical response up to 48 weeks of treatment.

Serious infections, malignancies, hypersensitivity reactions (including anaphylaxis and serum sickness) and major adverse cardiovascular events [MACE] are identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval.

Information on long term safety and the treatment of certain subpopulations of patients, as treatment of pediatric patients, patients with severe hepatic and renal impairment, patients pregnant and breastfeeding, treatment of the elderly is missing and is mentioned as missing information in the RMP.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infection Malignancy Serious hypersensitivity reactions (including anaphylaxis and serum sickness) Major adverse cardiovascular events (MACE)
Missing information	Use in paediatric patients Exposure during pregnancy Exposure during lactation Use in patients ≥65 years of age Use in patients with severe hepatic impairment Use in patients with severe renal impairment Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, ongoing, started**	**Date for submission of interim or final reports (planned or actual)**
CNTO1959PSO3001 /randomised controlled trial (category 3)	Long-term safety	Serious infection Malignancy Serious hypersensitivity reactions (including anaphylaxis and serum sickness) Major adverse cardiovascular events (MACE) Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis	Ongoing	Interim report: December 2016 Final report: May 2021
CNTO1959PSO3002 /randomised controlled trial (category 3)	Long-term safety	Serious infection Malignancy Serious hypersensitivity reactions (including anaphylaxis and serum sickness) Major adverse cardiovascular events (MACE) Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis	Ongoing	Interim report: December 2016 Final report: June 2021
Company-sponsored Observational Cohort Study/observational PASS – cohort study (category 3)	Long-term safety	Serious infection Malignancy Serious hypersensitivity reactions (including anaphylaxis and	Planned	Interim report: 4Q 2025 Final report: 4Q 2030

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, ongoing, started	Date for submission of interim or final reports (planned or actual)
		serum sickness) Major adverse cardiovascular events Exposure during pregnancy Use in patients ≥65 years of age Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis		
Electronic Administrative Health Claims Databases Review/observational PASS – cohort study (category 3)	Monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes during the first 6 six months following prenatal exposure to guselkumab	Exposure during pregnancy Exposure during lactation	Planned	Interim report: 4Q 2025 Final report: 4Q 2030
German Psoriasis Registry (PsOBEST Registry)/ observational PASS – cohort study (category 3)	Long-term safety	Serious infection Malignancy Serious hypersensitivity reactions (including anaphylaxis and serum sickness) Major adverse cardiovascular events Exposure during pregnancy Use in patients ≥65 years of age Long-term safety	Planned	Interim report: After enrolment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year) Final report: 4Q 2030

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, ongoing, started	Date for submission of interim or final reports (planned or actual)
		beyond 1 year in patients with moderate to severe plaque psoriasis		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks:		
None	None	None
Important potential risks:		
Serious Infection	SmPC: Guidance is provided in Posology and Method of Administration (4.2), Contraindications (4.3), and Special Warnings and Precautions for Use (4.4). INVENTED NAME is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation measures are proposed.
Malignancy	SmPC: Malignancy is not described in the SmPC. Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Serious hypersensitivity reactions (including anaphylaxis and serum sickness)	SmPC: Guidance is provided in Contraindications (4.3) and Special warnings and precautions for use (4.4). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Major adverse cardiovascular events	Tremfya is intended for use under the guidance and supervision of a	No additional risk minimization

(MACE)	physician experienced in the diagnosis and treatment of plaque psoriasis.	activities are proposed
Missing information:		
Use in paediatric patients	SmPC: Guidance is provided in Posology and Method of Administration (4.2). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Exposure during pregnancy	SmPC: Guidance is provided in Posology and Method of Administration (4.2) and Fertility, Pregnancy, and Lactation (4.6). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Exposure during lactation	SmPC: Guidance is provided in Posology and Method of Administration (4.2) and Fertility, Pregnancy, and Lactation (4.6). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Use in patients ≥65 years of age	SmPC: Guidance is provided in Posology and Method of Administration (4.2) and Pharmacokinetic Properties (5.2). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Use in patients with severe hepatic impairment	SmPC: Guidance is provided in Posology and Method of Administration (4.2). Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.
Use in patients with severe renal impairment	SmPC: Guidance is provided in Posology and Method of Administration (4.2). Tremfya is intended for use under the guidance and supervision of a physician experienced in the	No additional risk minimisation activities are proposed.

	diagnosis and treatment of plaque psoriasis.	
Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis	SmPC: Long-term safety beyond 1 year in patients with moderate to severe plaque psoriasis is not described in the SmPC. Tremfya is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.	No additional risk minimisation activities are proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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 list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. New Active Substance

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

The CHMP, based on the available data, considers guselkumab 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, Guselkumab Janssen-Cilag (guselkumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indication for guselkumab is as follows:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriasis is a chronic, non-communicable, painful, immunologically-mediated, disfiguring and disabling inflammatory skin disease for which there is no cure and with great negative impact on patients' quality of life (QoL).

3.1.2. Available therapies and unmet medical need

Despite the availability of multiple therapeutic modalities, the treatment of chronic moderate to severe psoriasis remains challenging. Although various topical treatments (eg, steroids, tar, anthralin [dithranol], calcipotriene, and tazarotene) are commonly used to treat milder cases of psoriasis, they are generally not suitable for treating more severe forms of the disease. Moreover, topical steroids can be associated with adverse events (AEs) such as skin atrophy, striae formation, suppression of the hypothalamic pituitary adrenal axis, and tachyphylaxis. Phototherapy (narrowband or broadband ultraviolet B [UVB] or the combination of psoralen [a photosensitizing drug] plus ultraviolet A light [PUVA]) is often effective and generally well tolerated but inconvenient (2 to 3 treatments weekly) and sometimes unavailable due to the need for specialized equipment. Therefore, compliance and subsequently efficacy are rarely sustained over the long-term. Toxicities include sunburn, photo-aging, and increased risk of skin cancer, particularly with PUVA.

Conventional systemic therapies include MTX, acitretin, and cyclosporine. Although effective, each is associated with significant toxicities, particularly organ damage with long-term administration, and each agent has recommended limitations for long-term administration. Rotational therapy is employed to minimize these significant side effects, though no evidence exists that rotational strategies can lessen the risk of serious adverse events (SAE). The chronicity of psoriasis, the cumulative toxicities of these agents and the restrictions with their lifetime use often make these agents unsuitable as a long-term solution. Apremilast, an oral selective inhibitor of the enzyme phosphodiesterase 4, was recently

approved for the treatment of psoriasis. Safety and tolerability concerns for apremilast include diarrhea, depression, weight decrease, and drug interactions.

A variety of biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, etanercept), an IL-12/23 antagonist (ustekinumab), and more recently, IL-17A inhibitors (secukinumab and ixekizumab). These agents are generally well-tolerated, and unlike conventional systemic agents, are not associated with cumulative toxicities that limit longer-term safety. However, as immunomodulatory agents they have the potential to increase risk for infection and malignancy. Concerns for anti-IL-17 class agents also include Crohn's disease, neutropenia, and mucosal candida infections.

While the response rates of available treatments, including those for more stringent measures of efficacy, have increased over time, there is still substantial room for improving the proportion of patients that achieve clear skin. In addition, the currently available treatments have practical limitations due to tolerability, toxicity, safety risks, and/or issues with ease of use or convenience.

3.1.3. Main clinical studies

The efficacy of guselkumab in the treatment of moderate to severe plaque psoriasis in adults is supported by analyses from 6 core psoriasis studies: two phase 1 studies: PSO1001 and PSO1002, one phase 2 dose-ranging study: PSO2001 (X-PLORE) and three phase 3 studies: PSO3001 (VOYAGE 1), PSO3002 (VOYAGE 2) and PSO3003 (NAVIGATE). Guselkumab treatment was compared with placebo and adalimumab treatment in both PSO3001 and PSO3002. Study PSO3003 examined the efficacy of guselkumab in subjects with an inadequate response to ustekinumab. The longer-term efficacy and safety of guselkumab is being assessed in 4-year extensions of studies PSO3001 and PSO3002 (ie, both studies will have an overall study duration of 5 years).

3.2. Favourable effects

In the 2 placebo- and adalimumab-controlled Phase 3 studies (PSO3001 and PSO3002), guselkumab 100 mg at Weeks 0, 4 and q8w thereafter demonstrated significant and clinically meaningful efficacy relative to placebo and adalimumab across multiple endpoints and subpopulations. The primary endpoints have been met: 70-73% of guselkumab-patients achieved PASI 90 response and 85% cleared or almost cleared (IGA 0/1 response). Corresponding data for placebo arm were 2.4-2.9% and for adalimumab treatment: 67% at week 16. Around 40% of guselkumab-patients attained complete clearing: the proportion of subjects achieving a PASI 100 response was 37.4% at Week 16, reached a maximum efficacy response of 49.8% by Week 32 and was maintained at Week 48 (47.4%) (Adalimumab: 26-28% at week 16). Clinical response was similarly robust at week 24, even some additional numerical improvement could be observed with guselkumab. Response could be maintained up to 48 weeks. The superior efficacy of guselkumab was evident across all endpoints and thresholds. Onset of effect was apparent from week 2, separation from adalimumab was evident from week 8 onwards.

Consistent improvements were observed across studies PSO3001 and PSO3002 in scalp psoriasis (ss-IGA 0/1: 80 vs. 10-15%), nail psoriasis (NAPSI% improvement: 35-39% vs. c.a.1), and hand or foot psoriasis (hf-PGA: 73-73% vs. 14%) in the guselkumab group compared with the placebo group at Week 16.

Across both studies (PSO3001 and PSO3002) significant improvements in patient-reported outcomes of DLQI (DLQI 0/1: 51-56% vs. 3-4%) and PSSD (clinically meaningful change in both symptom and sign scores: 73% vs. 4-14%) were observed in the guselkumab group compared with the placebo group. Significantly better improvements in patient-reported outcomes of DLQI (60% vs. 40%) and PSSD (clinically meaningful change: around 70% vs. 60%) were also observed in the guselkumab group compared with the adalimumab group at Week 24. The magnitude of improvements of these patient-reported outcomes from baseline within treatment groups was consistent between the 2 studies, and treatment differences were also consistent between the 2 studies.

At Week 48, a significantly greater proportion of subjects in the guselkumab maintenance group were PASI 90 responders compared with the withdrawal group (88.6% vs 36.8% $p<0.001$) in study PSO3002. Specifically, among PASI 90 responders randomized to withdrawal group, loss of PASI 90 response was evident as early as 4 weeks after withdrawal of therapy (Week 28) with the median time to loss of PASI 90 of 15.2 weeks. Among the PASI 90 responders in the placebo crossover, guselkumab, and adalimumab groups at Week 28, the proportion of subjects with a PASI 90 response began to decline in all groups by Week 32 (12 weeks after the last dose of guselkumab and 9 weeks after the last dose of adalimumab). The estimated median time to the loss of the PASI 90 response was approximately 16 weeks from Week 28 in the combined guselkumab group (including placebo crossover and guselkumab groups) and approximately 9 weeks in the adalimumab group.

Among the 112 subjects in the adalimumab group who were PASI 90 nonresponders at Week 28, 66.1% achieved a PASI 90 response by Week 48 after initiating guselkumab treatment Week 28.

Those subjects, who experienced loss of therapeutic effect (ie, loss of $\geq$ 50% of their Week 28 PASI improvement) after withdrawal from therapy, were followed for at least 4 weeks after reinitiating guselkumab. Within 4 weeks of re initiation of therapy, the majority of subjects (65%, 13/20) achieved a PASI 50 response.

In the randomised phase of study PSO3003, efficacy analyses based on the number of visits that subjects achieved predefined high levels of IGA or PASI responses (out of the 4 visits between Week 28 and Week 40) demonstrated that the guselkumab group achieved clinical responses approximately twice as often as the ustekinumab group ((1.5 visits and 0.7 visits respectively; $p<0.001$). Differences in response rate between guselkumab and ustekinumab treated subjects were noted as early as 4 weeks after subjects were randomized. From Week 16 through Week 40, the proportion of randomized subjects in the guselkumab group with IGA 0/1 and $\geq$ 2 grade improvement from Week 16, or PASI 90 responses increased from Week 16 through Week 36 and were maintained through Week 40. Separation of the response over time between the subjects randomized to the guselkumab group and the ustekinumab group was apparent as early as the first visit after randomization (Week 20) for the PASI 90 response or Week 24 for the IGA endpoint. The separation increased over time reaching a maximum at Week 40.

3.3. Uncertainties and limitations about favourable effects

Superiority to adalimumab was evident at almost all investigated aspects of psoriasis but improvement in nail psoriasis was not significantly different between the guselkumab and adalimumab groups in either studies as measured by f-PGA or NAPSI at Week 24.

Regarding re-treatment of psoriasis, the number of subjects who reached 8 weeks or longer after re-treatment was small and thus limits the interpretation of the results for re-treatment with guselkumab.

Psoriasis is a chronic disease and guselkumab is for long-term treatment. The data package available for the time being is, however, limited and further data on efficacy and safety and in particular immunogenicity are needed to fully characterise benefits from guselkumab treatment in the long-run (several studies or sub-studies are ongoing).

3.4. Unfavourable effects

Due to the IL-23 pathway blocking mechanism of action and available experience from similar compounds serious infections, malignancies, and cardiovascular events require special attention.

The most common adverse events were **infections and infestations**, represented mainly by nasopharyngitis, gastroenteritis, upper respiratory tract infections in nearly a fifth or a quarter of patients (21.3% / placebo, 23,2% / guselkumab and 24.6% / adalimumab) in the first 16 weeks, with slight increase to one third in frequency in guselkumab and adalimumab arms over the treatment course of 48 wk in the core psoriasis studies but with stable exposure-adjusted rate. Beyond 16wk treatment the need for antimicrobial therapy emerged for some infections in guselkumab and adalimumab groups, in a similar degree.

The rate of serious infections was low through Week 48 in the guselkumab (1.03/100 subject-yrs [95% CI: 0.49, 1.89]) and adalimumab (1.73/100 subject-yrs [95% CI: 0.75, 3.42]) groups, and consistent with the rate of these events reported for ustekinumab (0.93/100 subject-yrs).

History of latent TB was exclusion criterion; newly identified latent TB cases received concomitant TB treatment before or at initiation of study drugs in the trials. No active TB was observed in guselkumab treated patients, while two patients were identified with active TB on adalimumab arm in the core studies. This issue seems to be appropriately handled in the SmPC.

Malignancies are important safety aspects 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 for guselkumab regarding carcinogenicity. The pooled data from Phase 3 studies show malignancy rate similar to general population and to rates observed with other biologics in psoriasis trials. The event rates for Nonmelanoma skin cancer through Week 48 were 0.62/100 subject-yrs (95% CI: 0.23, 1.34) in the guselkumab group and 0.22/100 subject-yrs (95% CI: 0.01, 1.21) in the adalimumab group. Corresponding event rates for malignancies other than NMSC through Week 48 in these two treatment groups were 0.31/100 subj-yrs (95% CI: 0.06, 0.90) and 0/100 subject-yrs (95% CI: 0.00, 0.65), respectively. Through Week 48, there was a single NMSC in the adalimumab group (0.22/100 subject-yrs). This BCC event was reported for the active comparator-controlled period. There were no reports of NMSC through Week 48 in subjects who were crossed over from adalimumab to guselkumab (adalimumab/guselkumab group). Through Week 48, malignancies other than NMSC were reported for a total of 3 male subjects in the guselkumab group: the 2 events of prostate cancer reported through Week 28 and an event of invasive papillary breast carcinoma reported after Week 28. All 3 events resulted in discontinuation from study treatment as required by the protocol. With longer term follow-up (the Applicant completed Week 100 database locks for both the PSO3001 and PSO3002 studies with 723 subjects with at least 2 years of exposure to guselkumab) malignancies continue to occur infrequently among guselkumab-treated subjects, and the higher event rate of malignancies reported for the guselkumab group in comparison to the adalimumab group noted through the end of the original reporting period is no longer evident. However, considering the length of tumor induction still no firm conclusions concerning the possible etiology/causality of the observed malignant diseases can be made and malignancies are identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval.

Event rates on **cardiovascular** system were similar for MACE in guselkumab and adalimumab with 0.41 and 0.43/100 subject years, respectively. These patients had CV risk factors already at entry to the study. One fatal MI was reported from a Phase 2 study.

Clinical **haematology** laboratory evaluations showed few abnormalities according to CTCAE toxicity grade. Cellular elements and haemoglobin altered both directions around baseline values up to the 48wk cutoff period, while neutrophils and platelets showed only decrease. Few subjects in the guselkumab group had a laboratory value of CTCAE toxicity grade ≥2 through Week 16 (≤1.5%), Week 28 (<2.0%), or Week 48 (≤2.6%).

The proportion of subjects with injection-site reactions (ISR) following guselkumab injection through Week 16 or Week 48 was low (2.6%) however higher than in subjects receiving placebo (0.9%). Only 0.7 % of guselkumab injections were associated with an ISR through Week 48 (the rate of placebo injections with reported ISRs in the guselkumab treatment group was 0.3%). Almost all of the ISRs reported following guselkumab injection were assessed as mild, none were severe or considered serious, and none resulted in study drug discontinuation.

3.5. Uncertainties and limitations about unfavourable effects

So far up to two years' data are available on guselkumab therapy. It is uncertain if this period is long enough to fully characterize the favourable and unfavourable effects observed with guselkumab. 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.

The predominant adverse events were infections, the prevalence of which was similar in the placebo/guselkumab/adalimumab arm of the core psoriasis studies (Voyage 1 and 2) during the first 16 weeks, but later increased in the guselkumab and adalimumab arms - in a similar way, from a quarter to one-third. The exposure-adjusted infection AEs in the guselkumab group are considered to be stable throughout 48 weeks of exposure. As the mechanism of action of guselkumab may theoretically increase susceptibility to infections, long term follow-up data are needed to better understand the vulnerability to infections of guselkumab treated patients. Serious infections were identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval.

History of latent TB was an exclusion criterion; newly identified latent TB cases received concomitant TB treatment before or at initiation of study drugs in the trials. No active TB was observed in guselkumab treated patients, while two patients were identified with active TB on adalimumab arm in the core studies. This issue is appropriately handled in the SmPC.

The rate of malignancies was very low or none in Phase 3 studies, but in guselkumab groups somewhat higher than in adalimumab groups. However, the low number of events - close to near-normal rates - and the short observation period make difficult to draw any firm conclusion. The latest malignancy rates based on the pooled Week 100 data are consistent with those reported in the Day 121 responses and in the initial MAA, and are similar to those reported in the literature among patients with plaque psoriasis and with that observed for other treatments in patients with psoriasis. Serious infections, malignancies, hypersensitivity reactions (including anaphylaxis and serum sickness) and major adverse cardiovascular events [MACE] are identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval. However, considering the length of tumor induction still no firm conclusions concerning the possible

etiology/causality of the observed malignant diseases can be made and malignancies are identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval.

There were CV risk factors in patients with MACE in the pooled Voyage1 and -2 studies. In the ustekinumab inadequate responder PSO3003 study MACE events were higher in guselkumab than in ustekinumab groups and altogether higher than in the other Phase 3 studies.

Clinical haematology laboratory values assessed during the Phase 3 core psoriasis studies show decrease in neutrophil and platelet count, in a few patients (1.5-2.6%) up to Grade 2 of CTCAE scale. As cytokines play important role in immune function, infections and malignancies might be affected, therefore this uncertain information on neutropenia will be monitored post-marketing.

No subject exposed to guselkumab experienced anaphylactic reactions or serum sickness-like reactions. Whether guselkumab is associated with the risk serious hypersensitivity reactions (including anaphylaxis and serum sickness) is unknown based on the current data and this potential risk will be followed up post authorisation in the two clinical studies 3001 and 3002 as described in the RMP.

Since experience in patients $\geq$65 years of age is very limited, SmPC section 4.2 is updated to reflect this limitation.

In cases of three deaths were recorded in the clinical programme, one of which occurred in the guselkumab arm the patient with fatal MI had CV risk factors. Regarding mechanism of action of the investigated active substances, the cytokine blockade induced by guselkumab and ustekinumab may influence infections, malignancies and cardiovascular events.

There are no human data on transplacental exposure – which is comparable to maternal levels in cynomolgous monkeys – neither on exposure via lactation. Guselkumab could not be detected in milk of cynomolgous monkeys 28 days after injection. In humans, during the first few days after birth antibodies may be transferred to the newborns through milk. In this short period, a risk of guselkumab exposure to the breastfed child cannot be excluded.

Based on non-clinical and literature data transplacental exposure is not expected to interfere with development of immune system and with infant vaccinations.

3.6. Effects Table

Table 35 - Effects Table for guselkumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

Effect	Short Description Unit, CI	Treatment guselkumab 100 mg s.c. q8w	Control adalimumab	Control placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
PASI 90	90% reduction on PASI score at week 16 N (%) p value	PSO3001 241 (73.3%) < 0.001 PSO3002 347 (70.0%) < 0.001	PSO3001 166 (49.7%) < 0.001 PSO3002 116 (46.8%) < 0.001	PSO3001 5 (2.9%) PSO3002 6 (2.4%)	Guselkumab showed superior efficacy over placebo and adalimuab across the two adalimumab&placebo-controlled studies. Results were statistically significant and adjusted for multiplicity. Efficacy was consistent across studies and across several subgroups by demographics, geographics, disease characteristics and psoriasis medication history. The co-primary and all major secondary objectives were met, and a high percentage of patients had complete clearance of psoriatic plaques (PASI 100, IGA 0). Some minor issues need clarification, e.g. induction dose and rebound effects.	**Studies PSO2001, PSO3001 and 3002**
IGA 0/1	cleared or almost clear at week 16 N (%) p value	PSO3001 280 (85.1%) <0.001 PSO3002 417 (84.1%) <0.001	PSO3001 220 (65.9%) <0.001 PSO3002 168 (67.7%) <0.001	PSO3001 12 (6.9%) PSO3002 21 (8.5%)		
PASI 100	100% reduction on PASI score at week 16 N (%) p value	PSO3001 123 (38.1%) <0.001 PSO3002 169 (34.1%) <0.001	PSO3001 57 (17.4%) nc PSO3002 51 (20.6%) nc	PSO3001 1 (0.6%) PSO3002 2 (0.8%)		
IGA 0	cleared at week 16 N (%) p value	PSO3001 157 (47.7%) <0.001 PSO3002 215 (43.3%) <0.001	PSO3001 88 (26.3%) nc PSO3002 71 (28.6%) nc	PSO3001 2 (1.1%) PSO3002 2 (0.8%)		
DLQI (0,1)	Psoriasis had no effect on health-related quality of life at 16 weeks N (%) p-value	PSO3001 320 180 (56.3%) <0.001 PSO3002 491 254 (51.7%) <0.001	PSO3001 319 123 (38.6%) PSO3002 246 96 (39.0%) nc	PSO3001 168 7 (4.2%) PSO3002 246 8 (3.3%)		
Unfavourable Effects						
MACE through week 48	0.41/100	Per 100 PY	SC 100 mg, Wk0, 4, q8w	0.43/100 adalimumab, 0.00/100 placebo	Possible connection with treatment.	PSO3001, PSO3002

Effect	Short Description Unit, CI	Treatment guselkumab 100 mg s.c. q8w	Control adalimumab	Control placebo	Uncertainties/ Strength of evidence	References
Nasopharyngitis through week 48	19.6	%	SC 100 mg, Wk0, 4, q8w	20.1 adalimumab, 7.8 placebo		
Upper respirator tract infections through week 48	10.2	%	SC 100 mg, Wk0, 4, q8w	10.2 adalimumab, 4.5 placebo		
Oral herpes through week 48	1.6	%	SC 100 mg, Wk0, 4, q8w	1.5 adalimumab, 0.2 placebo		
Tinea pedis through week 48	1.1	%	SC 100 mg, Wk0, 4, q8w	0.2 adalimumab, 0.0 placebo		

Abbreviations: IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; DLQI = Dermatology Life Quality Index ; nc=not calculated
Notes: p-values in guselkumab column: comparisons between guselkumab and placebo p-values in adalimumab column: comparisons between guselkumab and adalimumab

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the two large placebo- and adalimumab-controlled Phase 3 studies guselkumab demonstrated significant and clinically meaningful efficacy relative to placebo and adalimumab. The primary endpoints have been met: 70-73% of guselkumab-patients achieved PASI 90 response and 85% cleared or almost cleared (IGA 0/1 response). Corresponding PASI 90 data for the placebo arm were 2.4-2.9% and for adalimumab treatment 46.8-49.7% at week 16.

Around 40% of guselkumab-patients attained complete clearing: the proportion of subjects achieving a PASI 100 response was 37.4% at Week 16 (adalimumab: 26-28% at week 16), reached a maximum efficacy response of 49.8% by Week 32 and was maintained at Week 48 (47.4%).

Clinical response was similarly robust at week 24, even some additional numerical improvement could be observed with guselkumab. Response could be maintained up to 48 weeks. The superior efficacy of guselkumab was evident across all endpoints and thresholds. Onset of effect was apparent from week 2; separation from adalimumab was evident from week 8 onwards.

At Week 48, a significantly greater proportion of subjects in the guselkumab maintenance group were PASI 90 responders compared with the withdrawal group (88.6% vs 36.8% $p<0.001$) in study PSO3002. Specifically, among PASI 90 responders randomized to withdrawal group, loss of PASI 90 response was evident as early as 4 weeks after withdrawal of therapy (Week 28) with the median time

to loss of PASI 90 of 15.2 weeks. Among the PASI 90 responders in the placebo crossover, guselkumab, and adalimumab groups at Week 28, the proportion of subjects with a PASI 90 response began to decline in all groups by Week 32 (12 weeks after the last dose of guselkumab and 9 weeks after the last dose of adalimumab).

Consistent improvements were observed in scalp psoriasis, nail psoriasis, and hand or foot psoriasis in the guselkumab group compared with the placebo group at Week 16 across studies PSO3001 and PSO3002 for subjects with an ss-IGA, f-PGA, and/or hf-PGA score $\geq$ 2 at baseline or with a NAPSI score >0 at baseline . In addition, in both studies, a significantly higher proportion of guselkumab subjects had scalp psoriasis and hand and foot psoriasis improvement compared with the adalimumab group at Week 24. Although guselkumab treatment resulted in substantial improvement of nail psoriasis, the effects observed were not significantly different between the guselkumab and adalimumab groups in either study as measured by f-PGA or NAPSI at Week 24.

Patient reported outcomes improved in parallel with the therapeutic effect.

Antibody development to guselkumab was low and the neutralizing types did not influence efficacy as measured by IGA and PASI responses at various thresholds.

Besides the significant therapeutic effect making even complete clearing possible (thereby significantly improving the quality of life of the patient) the adverse events are generally low in frequency, majority of them below 10%. Serious adverse events seem to be sporadic. Relationship of most AEs with guselkumab remains to be further clarified and refined as the low incidence, the relatively short, up to two years exposure is short for firm conclusions and further data will be generated post authorisation as described in the risk management plan.

The mechanism of action of guselkumab, inhibition of IL-23 pathway makes development of infections or autoimmun disease theoretically possible. Infections have been observed in low incidence and in similar or more favourable frequency and severity to active comparators so far. Targeted collection of data on characteristics, patterns, however, should be continued. With proper handling the therapeutic benefits of guselkumab seem evidently overweighing the risks.

Regarding malignancies the role of the cytokine-blockade might be multiple, and with near two years data the diagnosed malignancies in clinical trials were similar to those in the literature on plaque psoriasis patients and to those observed with other treatments for psoriasis This risk will be further monitored in post-marketing.

Effects of guselkumab on the cardiovascular system also remain to be explored in more detail in longer follow-up. Although reports only on sporadic cases are available so far which is insufficient to demonstrate association with guselkumab therapy, the event rate for all adjudicated CV events in the guselkumab group was comparable with that for the active comparator adalimumab in the clinical trials. (In the ustekinumab inadequate responder PSO3003 study MACE events were higher in guselkumab than in ustekinumab group).

These risks are adaequately covered by the SmPC. Serious infections, malignancies, hypersensitivity reactions (including anaphylaxis and serum sickness) and major adverse cardiovascular events [MACE] are identified as important potential risks and will be followed during the extension of the two clinical studies 3001 and 3002 post approval.

As there are no human data available on exposition of the foetus or newborn during pregnancy or lactation the use of guselkumab in these patients should be avoided or suspending breast feeding during guselkumab therapy considering the benefit and risk of either step should be considered.

Of note, there are nonclinical data on cynomolgous monkeys where the transplacental exposure is close to the maternal levels without apparent influence on the offspring, while guselkumab could not be detected in the breast milk 28 days after injection. Literature data suggest: in humans, during the first few days after birth antibodies may be transferred to the newborns through milk. *(Hanson et al., Ann. N.Y. Acad. Sci. 987: 199–206 (2003). Hurley and Theil, P.L.H. McSweeney and P.F. Fox (eds.), Advanced Dairy Chemistry, Volume 1A: Proteins: Basic Aspects, 4th Edition, DOI 10.1007/978-1- 4614-4714-6_9.)* In this short period, a risk of guselkumab exposure to the breastfed child cannot be excluded.

Transplacental exposure does not seem to interfere with development of immune system and with vaccinations.

3.7.2. Balance of benefits and risks

Statistically significant and highly clinically relevant short-term and longer-term efficacy of guselkumab has been shown. Potentially even total clearing of the psoriatic skin can be achieved in a considerable proportion of patients. This remarkable efficacy is accompanied by favourable tolerability and safety profile, with low rate of adverse events in clinical trials and with no sound pattern of serious adverse events which seem to be rather sporadic. The beneficial effects are considered to outweigh the unfavourable effects seen in the clinical programme.

Guselkumab is recommended to be given subcutaneously q8weeks and self-administration is also possible. This is generally convenient for the patients and may contribute to optimum compliance.

Long term efficacy and safety experience beyond two years is not available yet – careful follow up including focus on events involving the affected IL-23/IL-17 pathways will be done post authorisation by means of the long term extension of trials 3001 and 3002 as described in the RMP.

Unfavourable effects have been infrequently observed, and are mostly mild in severity. Therefore all the adverse events which might theoretically result from the mechanism of action of guselkumab or which were experienced with active substances with similar action should be carefully prospectively monitored, cases collected, analyzed and the information made available to the prescribers and patients. Malignancy, serious infections, serious hypersensitivity, cardiovascular events and suicidal ideation are the most important and appropriate information to grant marketing authorisation has been included in the product information.

The robust efficacy and the favourable safety profile with low incidence of adverse events makes the balance of benefits and risks for guselkumab positive.

3.8. Conclusions

The overall B/R of Tremfya is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the risk-benefit balance of Tremfya is favourable in the following indication:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults 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.

New Active Substance Status

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