CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761061Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761061
Priority or Standard	Priority
Submit Date(s)	November 16, 2016
Received Date(s)	November 16, 2016
PDUFA Goal Date	July 16, 2017
Division/Office	DDDP/ODE III
Review Completion Date	See DARRTS electronic signature page
Established Name	Guselkumab
(Proposed) Trade Name	TREMFYA
Pharmacologic Class	TREMFYA is an interleukin-23 blocker
Code name	CNTO 1959
Applicant	Janssen Biotech, Inc.
Formulation(s)	100 mg/mL guselkumab in a 1 mL single-dose prefilled syringe for subcutaneous use
Dosing Regimen	100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	TREMFYA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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ADL = Associate Director for Labeling
CDRH = Center for Devices and Radiological Health
COA = Clinical Outcomes Assessment
DARRTS = Document Archiving, Reporting and Regulatory Tracking System
DB III = Division of Biometrics III
DBRR I = Division of Biotechnology Research and Review 1
DCP 3 = Division of Clinical Pharmacology 3
DCRP = Division of Cardiovascular and Renal Products
DDDP = Division of Dermatology and Dental Products

DEPI = Division of Epidemiology
DIA = Division of Inspectional Assessment
DMA = Division of Monoclonal Antibodies
DMEPA = Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
DMQ = Division of Manufacturing Quality
DPM = Division of Pharmacometrics
DPMH = Division of Pediatrics and Maternal Health
DPP = Division of Psychiatry Products
DRISK = Division of Risk Management
OB = Office of Biostatistics
OBP = Office of Biotechnology Products
OCP = Office of Clinical Pharmacology
ODE III = Office of Drug Evaluation III
OND = Office of New Drugs
OPDP = Office of Prescription Drug Promotion
OPF = Office of Process and Facilities
OPQ = Office of Pharmaceutical Quality
OPRO = Office of Program and Regulatory Operations
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
OTS = Office of Translational Sciences
PLT = Patient Labeling Team
PM = Project Manager
QT-IRT= QT-Interdisciplinary Review Team
RBPMBI = Regulatory and Business Process Management Branch I
SRPM = Safety Regulatory Project Manager

Glossary

AC	advisory committee
ADA	anti-drug antibodies
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARIA	Active Risk and Identification Analysis
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	Area under the curve
BCC	basal cell carcinoma
BLA	biologics license application
BMI	Body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
BW	boxed warning
CABG	coronary artery bypass graft
CBER	Center for Biologics Evaluation and Research
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CDC	complement dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CD4+	cluster of differentiation 4 positive
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
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CFR	Code of Federal Regulations
CHF	congestive heart failure
CHO-K1	Chinese hamster ovary cells, subclone K1
CI	Confidence interval
cIEF	capillary isolelectric focusing
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CO_2	carbon dioxide
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CQA	critical quality attribute
CRF	case report form
CRO	contract research organization
CRT	clinical review template
cSDS	capillary sodium dodecyl sulfate
CSR	clinical study report
CSS	Controlled Substance Staff
CV	Cardiovascular
DHOT	Division of Hematology Oncology Toxicology
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee

DMSO	dimethyl sulfoxide
DP	drug product
DS	drug substance
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
ELISA	enzyme linked immunosorbent assay
EOP2	End of Phase 2
EP	erythrodermic psoriasis
ePPND	enhanced pre- and post-natal development
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FOCBP	females of child-bearing potential
GC-MS	gas chromatography- mass spectrometry
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GLP	good laboratory practice
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
GPP	generalized pustular psoriasis
GRMP	good review management practice
HDL	high density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
HMW	high molecular weight
HPLC-UV-MS	high performance liquid chromatography-ultraviolet-mass spectrometry
HSV	Herpes simplex virus
HUA	hospitalization for unstable angina
HV	healthy volunteers
ICF	informed consent form
ICH	International Conference on Harmonization
ICP-MS	inductively coupled plasma-mass spectrometry
IFU	instructions for use
IGA	Investigator's Global Assessment
IgG1λ	Immunoglobulin G1 lambda
IL1α	interleukin 1 alpha
IL-17A	interleukin 17A
IL-23	interleukin 23
IND	Investigational New Drug
IP-10	interferon-inducible protein 10
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISR	Injection site reaction
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LDL	low density lipoprotein
LMW	low molecular weight
LOCF	last observation carried forward

LOQ	limit of quantitation
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MCB	Master Cell Bank
MCP-1	Monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MG	medication guide
MI	multiple imputation, myocardial infarction
mITT	modified intent to treat
[redacted] (b) (4)	
MRHD	maximum recommended human dose
[redacted] (b) (4)	
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NMSC	non-melanoma skin cancer
NOAEL	no observed adverse event level
NRI	non-responder imputation
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
NSTEMI	non-ST-elevation myocardial infarction
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASI	Psoriasis Area and Severity Index
PASI 75	At least a 75% improvement from Baseline in the PASI
PBMC	peripheral blood mononuclear cells
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
[redacted] (b) (4)	
PFS	pre-filled syringe
[redacted] (b) (4)	
PFS (b) (4)	[redacted] (b) (4) Passive Delivery System
PGA	Physician's Global Assessment
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PML	periventricular multifocal leukoencephalopathy
PMR	postmarketing requirement
PP	per protocol
PPD	postpartum day
PPI	patient package insert
PPP	palmoplantar pustulosis
PREA	Pediatric Research Equity Act
PRM	primary reference material
PRO	patient reported outcome
PS-80	polysorbate 80

PsA	psoriatic arthritis
PSD	Psoriasis Symptom Diary
PSSD	Psoriasis Symptom and Sign Diary
PSUR	Periodic Safety Update report
PT	Preferred term
PUVA	Psoralen and ultraviolet-A
QTc	Corrected QT interval
RA	rheumatoid arthritis
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RNS	rigid needle shield
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCC	squamous cell carcinoma
SE-HPLC	size exclusion high performance liquid chromotography
SGE	special government employee
SIB	suicidal ideation and behavior
SOC	System organ class
STAT	signal transducer and activator of transcription
STDM	Study Data Tabulation Model
TB	tuberculosis
TDAR	T-cell dependent antibody response
Th-17	T-Helper 17 cell
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TK	toxicokinetic
TNF	tumor necrosis factor
ULN	Upper limit of normal
URI	upper respiratory infection
USP	United States Pharmacopeia
UVB	ultraviolet B
	(b) (4)
VTE	venous thromboembolic event
W&P	Warnings and Precautions
WBC	white blood cell
WCB	Working Cell Bank
WRM	working reference material

1 Executive Summary Office Level Concurrence

Janssen Biotech, Inc. submitted BLA 761061 for TREMFYA (guselkumab) injection, a new molecular entity (NME), in support of an indication for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Guselkumab, the active ingredient in TREMFYA, is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds to the p19 subunit of interleukin 23 (IL 23) and inhibits its interaction with the IL 23 receptor. IL 23 is a naturally occurring cytokine involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines implicated in the pathogenesis of psoriasis.

To support an efficacy claim for TREMFYA (guselkumab) injection for the treatment of psoriasis, the applicant conducted two Phase 3 clinical trials, Trial 3001 (VOYAGE 1) and Trial 3002 (VOYAGE 2). Enrolled subjects had a score of moderate or severe (≥3) on the Investigator's Global Assessment (IGA) scale, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. About 75% of subjects had moderate disease at baseline. In both trials, subjects were randomized to guselkumab (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), to placebo, or to adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter.

The co-primary endpoints for both trials were the proportion of subjects who achieved an IGA score of 0 ("cleared") or 1 ("minimal"), and the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90), at Week 16. Efficacy of guselkumab was convincingly demonstrated on both IGA (3001: 85% vs 7% and 3002:84% vs 8%) and PASI 90 (3001:73% vs 3% and 3002: 70% vs 2%) when compared to placebo at Week 16. Comparisons between guselkumab and US licensed adalimumab were secondary endpoints at Week 16 (IGA, PASI 90, and PASI 75) and Week 24 (IGA, and PASI 90). In both trials, guselkumab was statistically superior for all pre-specified secondary efficacy endpoints.

The primary safety database of pooled data from the two Phase 3 trials was adequate to characterize the safety profile of TREMFYA (guselkumab) injection. In general, TREMFYA (guselkumab) injection appeared to be well tolerated. Adverse reactions occurring in ≥ 1% and observed more frequently in subjects receiving TREMFYA (guselkumab) injection through Week 16 included headache, injection site reactions, arthralgia, diarrhea and elevated liver enzymes. Similar to the safety profile of other approved systemic biologic therapies approved for psoriasis, infections appeared to occur more frequently in subjects receiving TREMFYA (guselkumab) injection as compared to subjects who received placebo (23% vs 21% through Week 16). Infections reported more frequently with guselkumab included upper respiratory infections, gastroenteritis, tinea and herpes simplex infections. All cases were mild to moderate in severity and did not lead to discontinuation. Risk of infection, the risk of latent TB reactivation, and the recommendation to avoid live vaccines will all be included in the Warnings and Precautions section of product labeling.

The overall incidence of development of antibodies to guselkumab (ADA+) after up to 52 weeks of exposure to guselkumab was 5.5% in the Phase 2 and Phase 3 clinical trials. Of the 96 subjects who were antibody positive, 7 subjects (7.3%) were positive for neutralizing antibodies (NAbs). Immunogenicity may have a negative impact on systemic exposure of guselkumab: comparison of the steady state trough concentration data within each ADA+ subject before and after the development of antibodies (i.e., within-subject comparison) indicated that steady state

trough guselkumab levels can be reduced in ADA+ subjects. This effect wasn't consistent across all ADA+ subjects and appeared unrelated to the antibody titer.

Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a safety signal. Treatment with guselkumab was not associated with an increased incidence of the safety concerns of suicidal ideation and behavior (SIB) or major adverse cardiovascular events (MACE). No serious hypersensitivity reactions such as anaphylaxis were reported in subjects who received guselkumab, although several subjects reported urticaria. Based on the mechanism of action, post-marketing safety studies to assess the risk of malignancy and other serious adverse events, as well as risk of fetal exposure, will be required.

I concur with the recommendation of the Division of Dermatology and Dental Products to approve TREMFYA (guselkumab) injection for the treatment of moderate to severe psoriasis in patients who are candidates for phototherapy or systemic therapy. The safety concerns identified with TREMFYA use can be adequately managed by professional labeling, including a Medication Guide, and routine pharmacovigilance.

1.1. Product Introduction

TREMFYA (guselkumab) injection, for subcutaneous use is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23), and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines. Guselkumab is a new molecular entity (NME). The proposed indication is treatment adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed dose is 100 mg at Weeks 0 and 4, then every 8 weeks (q8w) thereafter administrated by subcutaneous injection. The proposed commercial presentation for guselkumab drug product (100 mg/mL) is a single-use pre-filled syringe (PFS) with a 1.0 mL fill volume.

The Agency concluded that the proposed proprietary name, TREMFYA, was acceptable from both a promotional and safety perspective under BLA 761061 [Proprietary Name Review by Carlos M Mena-Grillasca, RPh, Division of Medication Error Prevention and Analysis (DMEPA) dated 4/19/2017].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from two adequate and well-controlled trials [Trial 3001 (VOYAGE1) and Trial 3002 (VOYAGE2)], which provided evidence of the effectiveness of guselkumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Both trials assessed the changes from baseline to Week 16 compared to placebo in the two co-primary endpoints:

- the proportion of subjects who achieved an Investigator's Global Assessment (IGA) score of 0 ("cleared") or 1 ("minimal")
- the proportion of subjects who achieved at least a 90% reduction in the Psoriasis Area and Severity Index (PASI) composite score (PASI 90)

Guselkumab was statistically superior to placebo (p-values < 0.001) on the co-primary endpoints in both trials. The applicant has demonstrated that guselkumab is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. TREMFYA (guselkumab) injection, for subcutaneous use is proposed for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Guselkumab, the active ingredient in TREMFYA, is a new molecular entity. Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines that has been implicated in the pathogenesis of psoriasis. Guselkumab is available as 100 mg/mL in single-dose prefilled syringe..

For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and brodalumab). Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office based administration requirements. All of the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression.[1] Because of these limitations, there is a recognizable need for additional therapeutic options despite the number of available therapies.

Substantial efficacy was demonstrated in two pivotal Trial 3001 (VOYAGE 1) and Trial 3002 (VOYAGE 2), which enrolled 1443 adult subjects with moderate- to- severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. In both trials, subjects were randomized to either guselkumab (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), placebo or US licensed adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter).The co-primary endpoints were i) the proportion of subjects who achieved an IGA score of 0 ("cleared") or 1 ("minimal"), and ii) the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90), both assessed at Week 16. In Trials 3001 and 3002, guselkumab was superior to placebo on both IGA (Trial 3001: 85% vs 7% and Trial 3002:84% vs 8%) and PASI 90 (Trial 3001:73% vs 3% and Trial 3002: 70% vs 2%) at Week 16. Comparisons between guselkumab and US licensed adalimumab were assessed as secondary endpoints at Week 16 (IGA, PASI 90, and PASI 75) and Week 24 (IGA, and PASI 90). The results of an analysis

[1] Menter A 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;58:826-50.

of all the North America sites (i.e., U.S. and Canada), demonstrating superiority of TREMFYA to U.S. licensed adalimumab.
To evaluate maintenance and durability of response (Trial 3002), subjects randomized to guselkumab at Week 0 and who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (i.e. receive placebo). At Week 48, 89% of subjects who continued on guselkumab maintained PASI 90 compared to 37% of subjects who were re-randomized to placebo and withdrawn from guselkumab. For responders at Week 28 who were re-randomized to placebo and withdrawn from guselkumab, the median time to loss of PASI 90 was approximately 15 weeks.

The primary safety database, which consisted of data from the pooled Phase 3 Trials 3001 and 3002, was adequate to characterize the safety profile of TREMFYA (guselkumab) injection. Based on the analysis of the submitted data, treatment with guselkumab did not appear to increase the risk of mortality. The majority of serious adverse events (SAEs) were single events with no identifiable pattern. Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a safety signal. Treatment with guselkumab was not associated with an increased incidence of suicidal ideation and behavior (SIB) or major adverse cardiovascular events (MACE). No cases of active tuberculosis occurred in the development program and no serious hypersensitivity reactions such as anaphylaxis were reported in subjects who received guselkumab. However, infections such as upper respiratory infections, gastroenteritis, tinea and herpes simplex (HSV) infections occurred more frequently in subjects who received guselkumab compared to subjects who received placebo (23% vs 21% through Week 16). All cases were mild to moderate in severity and did not lead to discontinuation of guselkumab. Other adverse reactions, occurring in ≥ 1% and observed more frequently in subjects receiving guselkumab through Week 16, included headache, injection site reactions, arthralgia, diarrhea and elevated liver enzymes. These identified adverse reactions will be conveyed in product labeling. However, post-marketing safety studies to assess the risk of malignancy and other serious adverse events, as well as risk of fetal exposure, are recommended.

Prescription and patient labeling, including a Medication Guide, as well as pharmacovigilance are adequate to manage the risk of TREMFYA in the postmarketing milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended postmarketing requirements under 505(o): fetal exposure studies and a safety study to assess for malignancy and other serious adverse reactions (e.g. serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events), and required pediatric assessment, Pediatric Research Equity Act (PREA) (21 U.S.C. 355c): a safety, efficacy and PK study in pediatric subjects 6 years to < 18 years of age with moderate to severe plaque psoriasis.

The available safety and efficacy data supports the approval of TREMFYA (guselkumab) injection for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Although there are a number of FDA-approved products with an acceptable risk-benefit profile for this indication, none of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3 %, of which an estimated 20% have moderate to- severe disease. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.[1]	Moderate-to-severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	• FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekezumab), IL-17A receptor antagonist (brodalumab), T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). • All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product.	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of moderate-to severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Data from Trial 3001 and Trial 3002 provided substantial evidence of the effectiveness of guselkumab for the treatment of moderate to severe plaque psoriasis. These trials enrolled 1443 adult subjects with moderate to severe plaque psoriasis defined as Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. In both trials, subjects were randomized to either guselkumab (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), placebo or US licensed adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter).The co-primary endpoints were i) the proportion of subjects who achieved an IGA score of 0 ("clear") or 1 ("minimal"), and ii) the proportion of subjects who achieved at least a 90% reduction in the PASI composite score (PASI 90), both assessed at Week 16. • In Trials 3001 and 3002, guselkumab was superior to placebo on both IGA (3001: 85% vs 7% and 3002:84% vs 8%) and PASI 90 (3001:73% vs 3% and 3002: 70% vs 2%) at Week 16. Comparisons between guselkumab and US licensed adalimumab were secondary endpoints at Week 16 (IGA, PASI 90, and PASI 75) and Week 24 (IGA, and PASI 90).	The data submitted by the applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a patient with moderate-to-severe plaque psoriasis treated with 100 mg guselkumab at Week 0, 4 and every 8 weeks is likely to achieve clear or almost clear skin by Week 16, and to maintain this effect with continued treatment to Week 48.
Risk	• The primary safety database (Trials 3001 and 3002) included 1367 subjects who received guselkumab at the proposed dose of 100 mg SC and dosing regimen (Weeks 0 and 4, then every 8 weeks thereafter). Of these 1367 subjects, 1036 subjects were treated for 6 months, and 592 subjects received treatment for 1 year. The safety database is adequate and consistent with other products approved for the proposed indication. • Infections occurred more frequently in subjects who received guselkumab compared to subjects who received placebo (23% vs	The safety profile of guselkumab has been adequately characterized. At this time, the safety profile appears to be similar to ustekinumab, the approved a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. The safety profiles for all of the approved therapies are informed by post marketing data, which is not yet available for guselkumab. However, in view

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	21% through Week 16). Upper respiratory infections, tinea and herpes simplex (HSV) infections occurred more frequently in subjects exposed to guselkumab. • Treatment with guselkumab was not associated with an increased incidence of AE in the categories of suicidal ideation and behavior (SIB) and major adverse cardiovascular events (MACE). • No cases of active tuberculosis occurred in the development program in subjects who received guselkumab. Subjects were screened for tuberculosis prior to enrollment in the pivotal trials, and screening is recommended in product labeling. • Serious hypersensitivity reactions such as anaphylaxis were not observed in subjects exposed to guselkumab although rarely urticarial reactions were reported. • There is no data on the use of guselkumab in pregnant women. In nonclinical reproductive toxicity study in cynomolgus monkeys, neonatal deaths occurred following treatment of the pregnant females at 6 to 30 times the Maximum Recommended Human Dose (MRHD).Two postmarketing studies are recommended to characterize the risk of fetal exposure to guselkumab.	of the premarket safety database for guselkumab and the mechanism of action, it is unlikely that postmarketing exposure will identify risks for malignancy or specific organ toxicities of a magnitude that would alter the risk-benefit conclusion.
Risk Management	• The following PMRs (1-4) and PMC (5,6) are recommended: 1. Conduct a prospective registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to guselkumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.	Prescription labeling, patient labeling (including Medication Guide) and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2. Conduct a retrospective cohort study using claims or electronic medical record data or a case-control study to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to guselkumab during pregnancy compared to an unexposed control population. 3. Conduct an observational study to assess the long-term safety of guselkumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the guselkumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 6 year period and follow for a minimum of 8 years from the time of enrollment. 4. Conduct a pharmacokinetics (PK), safety and efficacy study in pediatric subjects 6 years to <18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	guselkumab of at least one year). 5. Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA. 6. Provide additional data comparing th (b) (4) Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the (b) (4) . • Labeling: Prescription labeling adequately addresses the risks identified during product development and conveys the lack of data from human exposure during pregnancy. A Medication Guide and Instructions for Use for the proposed presentation are included in patient labeling and are appropriate to inform patients of potential risks. • A REMS is not recommended. Precedent biologic products with comparable safety profiles have a similar approach to post-marketing risk management.	

2 Therapeutic Context

Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution.[2] Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.[3]

In the US and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively.[2] It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of psoriasis patients.[4]

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The age of onset is earlier in women than in men.[2]

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis.. A diagnosis of psoriasis can be made by history and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions.[2]

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults.[2]

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[2] Feldman, Steven R., MD. PhD; Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis; UpToDate.com; updated December 9, 2015
[3] Blauvelt, Andrew and Ehst, Benjamin D, Pathophysiology of Psoriasis; UpToDate.com; updated July 8, 2015
[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS 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 May;58(5):826-50.

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders.[5]

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social and emotional impact including: depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed need to enhance the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as women during pregnancy and pediatric patients.

2.2. Analysis of Current Treatment Options

Analysis of Current Treatment Options

Although there are multiple topical therapies available for the treatment of psoriasis, topical therapies are not typically used alone for the treatment of moderate to severe disease. Approved systemic therapies for the treatment of moderate to severe plaque psoriasis are described in the table below.

[5] Korman, Neil; Comorbid Disease in Psoriasis; UpToDate.com; updated March 24, 2017.

Table 1: Summary of Treatment Armamentarium for Moderate to Severe Psoriasis

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments					
Antimetabolite/ Immunosuppressant					
Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; *but only when diagnosis established, by biopsy and/or dermatologic consultation.* Must rule out undiagnosed concomitant disease affecting immune responses.	Starting Dose Schedules 1. Weekly single oral, intramuscular (IM) or intravenous (IV) dose schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/wk should not ordinarily be exceeded.	No efficacy information for psoriasis in the label.	Boxed Warning (BW)- potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID[6] Tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis"	Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphopro-liferative disorders; Recommend Periodic liver biopsy if tx long-term Pregnancy: X
Tumor Necrosis Factor Inhibitors					
Infliximab (Remicade) 2006	Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate.	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks	From the label: 3 R,DB,PC[7] trials PASI75 at week 10 1-Inflix[8] (5mg/kg)- 80% vs 3% placebo 2- Inflix (5mg/kg)- 75% vs 2% placebo 3- Inflix (5mg/kg)- 88% vs Inflix (3mg/kg) 72% vs 6% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	Pregnancy: B

[6] Non-steroidal anti-inflammatory drug
[7] R=randomized, DB=double-blind, PC= placebo-controlled
[8] Inflix=infliximab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg via subcutaneous injection (SC) initial dose, followed by 40 mg SC every other week starting one week after initial dose	From the label: 2 R, DB, PC[5] trials PASI75 at week 16 1-Ada[9]-71% vs 7% placebo 2- Ada-78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma Warnings: hypersensitivity reactions, Hep B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome	Pregnancy: B
Etanercept (Enbrel) 2004; 2016	Chronic moderate to severe psoriasis, candidates for photo- therapy or systemic therapy; 11/2016- approved for patients 4 years of age and older	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly	From the label: 2 R, DB, PC5 trials PASI75 at 3 months 1-Etan[10]-47% vs 4% placebo 2-Etan-46% vs 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, Hep B reactivation	Pregnancy: B
IL-12 and IL-23 blocker					
Ustekinumab (Stelara) 2009	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	For patients weighing <100 kg :45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks For patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From the label: 2 R, DB, PC trials PASI75 at week 12 1-uste[11](90mg)-66% vs uste(45mg)-67% vs 3% placebo 2-uste (90mg)-76% vs uste(45mg)-67% vs 4% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	Pregnancy: B
IL- 17A blocker					
Secukinumab (Cosentyx) 2015	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	300 mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of	From the label: 4 R, DB, PC trials PASI75 at week 12 1-sec[12] (300mg)-82% vs sec (150mg)-71% vs 4%	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease,	Pregnancy: B

[9] Ada=adalimumab
[10] Etan= etanercept
[11] Uste=ustekinumab
[12] Sec= secukinumab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
		150 mg may be acceptable	placebo 2-sec (300mg)-76% vs sec (150mg)-67% vs 5% placebo 3-sec (300mg)-75% vs sec (150mg)-69% vs 0% placebo 4-sec (300mg)-87% vs sec (150mg)-70% vs 3% placebo	hypersensitivity reactions, pretreatment eval for TB.	
Ixekizumab (Taltz) 2016	moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or photo-therapy	160 mg (two 80 mg injections) SC at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From the label: 3 R, DB, PC trials PASI75 at Week 12 1: Ixe (80 mg q2wk) 89% vs 4% placebo 2: Ixe (80 mg q2wk) 90% vs 2% placebo 3: Ixe (160 mg x 1, then 80 mg q2wk) 87% vs 7% placebo	W&Ps: Infections (Upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB.	
IL- 17 Receptor A antagonist					
Brodalumab (Siliq) 2017	moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies	210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks	From the Label: 3 R, DB, PC trials PASI 75 and sPGA of 0 ("clear") or 1 ("almost clear") at Week 12 1: Bro (210 mg q2wk) PASI 75 83% vs 3% placebo; sPGA 0 or 1 Bro 76% vs 1% placebo 2: Bro (210 mg q2wk) PASI 75 86% vs 8% placebo; sPGA 0 or 1 Bro 79% vs 4% placebo; PASI 100 Bro 44% vs Uste 22% 3: Bro (210 mg q2wk) PASI 75 85% vs 6% placebo; sPGA 0 or 1 Bro 80% vs 4% placebo; PASI 100 Bro 37% vs Uste 19%	Box warning for Suicidal Ideation and Behavior W&Ps: Suicidal ideation and behavior; Infections (serious infections and fungal infections); Crohn's disease; pretreatment eval for TB; avoid live vaccines.	REMS requires prescribers and pharmacies to be certified; patients must sign a Patient-Prescriber agreement form
T-Cell Inhibitor/ Immunosuppressant					
Cyclosporine 1997	Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI75 - 51% at 8 weeks, 79% at 16 weeks	BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of	Pregnancy Category C

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	least one systemic therapy			neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx-↑ risk of skin malignancies Warnings: Hepatotoxicity, hyper-kalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy (PML), malignancies, serious infection, neurotoxicity	
Retinoid					
Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments	Starting dose: 25 to 50 mg orally (PO) per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	From the label: 2 DB, PC trials-Mean change in PGA at 8 weeks A-Acitretin(50mg)-2 vs -0.29 on placebo B- Acitretin (50mg)-1.57 vs Acitretin (25 mg)-1.06 vs -0.06 on placebo (no multiplicity adjustment for trial B)	BW-pregnancy must be prevented during Rx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @ FDA for details. Patients cannot donate blood for 3 years post Rx, See label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologi c effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression Pregnancy category X
Phosphodiesterase 4 (PDE4) inhibitor					
Apremilast (Otezla) 2014	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg PO twice daily	From the label: 2 R, DB, PC trials PASI75 at 16 weeks 1- aprem[13]33% vs 5% in placebo 2- aprem 28.8% vs 5.8% in placebo	W&P: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin)	Diarrhea, nausea, URI, headache Pregnancy Category C
Phototherapy					
PUVA-8-MOP (methoxsalen)	Severe, recalcitrant,	20 -70 mg PO (based on weight)	No efficacy information for	BW: Should only be used by MDs who have	Nausea, erythema,

[13] aprem=apremilast

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
+ UVA therapy	disabling psoriasis not responsive to other forms of therapy	taken 2-4 hours before exposure to UVA light	psoriasis in the label.	special competence in psoriasis management Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion; Pregnancy category C

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because guselkumab is a new molecular entity (NME) and is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant developed guselkumab injection under IND 105004 which was submitted on April 30, 2009. During their development program, the applicant interacted with the Agency at the following milestones meetings [Guidance meetings 6/3/11, 11/16/11,6/26/13, and 1/27/16; End-of-Phase 4/9/14; Pre-BLA meeting 4/6/16].

During a Guidance meeting on November 16, 2011, the applicant and the Agency discussed the proposed clinical development plan intended to support guselkumab registration (b) (4) .

During a Guidance Meeting on June 26, 2013, the applicant and the Agency discussed the development of a novel patient reported outcome (PRO), a Psoriasis Symptom Diary (PSD), to assess the severity of the symptoms of moderate to severe psoriasis (as a secondary endpoint).

An End-of-Phase 2 (EOP2) meeting was held on April 9, 2014. In the meeting package, the applicant submitted results from their Phase 2 dose-ranging trial (CNTO1959PSO2001) and protocol outlines for the following Phase 3 trials:

1. **Trial CNTO1959PSO3001**: a Phase 3, multicenter, randomized, double-blind, active comparator-controlled trial, evaluating the efficacy and safety of guselkumab vs. adalimumab (HUMIRA®) in the treatment of subjects with moderate to severe plaque-type psoriasis; to include 400 subjects who have plaque-type psoriasis for at least 6 months and who are candidates for phototherapy or systemic therapy. No placebo arm was included in the original protocol for this trial.

2. **Trial CNTO1959PSO3002**: a Phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled (adalimumab) trial evaluating the efficacy and safety of guselkumab in the treatment of subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment to include 1000 subjects who have plaque-type psoriasis for at least 6 months and who are candidates for phototherapy or systemic therapy.

3. **Trial CNTO1959PSO3003**: a Phase 3, multicenter, randomized, double-blind trial evaluating the efficacy and safety of guselkumab vs. ustekinumab (STELARA®) in the treatment of subjects with moderate to severe plaque-type psoriasis who have had an incomplete response ((b) (4) at Week 16) to treatment with STELARA; to include 800 subjects who have plaque-type psoriasis for at least 6 months and who are candidates for phototherapy or systemic therapy. No placebo arm was included in the original protocol for this trial.

During the meeting, the Agency noted that the proposed Phase 3 trials have different designs, different time-points for efficacy evaluation and different endpoints. Extensive comments regarding these trials were conveyed to the applicant (meeting minutes dated April 15, 2014).

On May 19, 2014, the applicant submitted modified trial designs to address Agency comments. Modifications included: addition of a placebo arm to Trial 3001, trial endpoints, time-points for comparison and incomplete response definition (i.e., changed it to IGA≥2). In an advice letter (May 30, 2014), Agency advised the applicant that the modified clinical development program seems reasonable. The Agency encouraged the applicant to submit full trial protocols to receive detailed feedback on clinical trial design and statistical analysis plans.

Additionally, at the EOP2 meeting the Agency noted discrepancies regarding PK comparability between formulations (lyophilized vs liquid drug product) and between the devices proposed for use in the Phase 3 trials. The devices in question were the (b) (4) (PFS (b) (4). The applicant decided to proceed with the Phase 3 trials using the PFS (b) (4)

The applicant submitted the full protocol for Trials 3001, 3002, and 3003 in July 2014. FDA responded with extensive comments regarding the trial design, endpoints and the proposed statistical analysis plan (SAP) (Advice letter, October 15, 2014).

On February 19, 2015, the applicant submitted amended protocols for Trials 3001, 3002, and 3003. The amendments to the protocols did not address any of the statistical comments conveyed in the advice letter sent to the applicant on October 15, 2014. At the time of submission, all three trials were already underway; therefore, some of the statistical comments could not be addressed. An advice letter was sent to the applicant on April 27, 2015. The letter stated the following:

> "You have submitted amended Phase 3 protocols (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003); however, it appears that you have started enrollment in the trials without addressing many of the comments and recommendations conveyed in the advice letter dated October 15, 2014. In particular, we refer you to comments regarding the investigation of the center-to-center variability, analysis populations, handling of missing data and efficacy endpoints (Trial CNTO1959PSO3003) as these comments and recommendations pertain to the interpretability of trial findings."

On June 17, 2015, the applicant submitted the SAP for Trial 3003, followed by the SAPs for Trials 3001 and 3002 on July 2, 2015. In the cover letter for both of these submissions, the applicant stated that the purpose of the submission is to notify Agency how they plan to address the advice letter dated April 27, 2015 regarding Trials 3001, 3002, and 3003. Specifically, the applicant stated that the "analysis-related" comments are addressed in the SAPs for each trial. In addition, the applicant stated that the "non-analysis related" comments will be addressed in the submission documents as part of the Biologic Licensing Application (BLA). The Agency responded with comments regarding two secondary efficacy endpoints, which were based on the patient reported outcome Psoriasis Symptom and Sign Diary (PSSD). The Agency advised that it is not clear whether the PSSD is a validated PRO and whether it is appropriate to average the five symptom items (i.e., itch, pain, stinging, burning, and skin tightness). In addition, the Agency advised that it is not clear whether absolute change or at least a 1-point change is clinically meaningful. The Agency commented that itch (i.e., one of the components of the PSSD) is an important symptom to patients with plaque psoriasis; therefore, the evaluation of pruritus may represent a relevant, clinically meaningful secondary endpoint. The Agency recommended that the applicant propose a responder definition which would be clinically

meaningful (e.g., 4-point change on an 11-point NRS PRO for itch) (Advice letter, February 22, 2016).

None of the trials in the development program for guselkumab were conducted under a Special Protocol Assessment (SPA).

At the Pre-BLA meeting (April 6, 2016), Agency and the applicant discussed the content, format, and submission strategy for the guselkumab BLA submission. The BLA will include three main Phase 3 trials (Trials 3001, 3002 and 3003). The objectives of Trials 3001 and 3002 are to establish the efficacy of guselkumab (i.e., guselkumab vs. placebo) and to establish comparative efficacy claims [i.e., guselkumab vs. Humira (adalimumab)]. Trial 3002 will provide data regarding withdrawal and retreatment with guselkumab (i.e., only Trial 3002 contained a maintenance period). The objective of Trial 3003 is to provide data regarding the efficacy of guselkumab in subjects with inadequate response to Stelara® (ustekinumab). It should be noted that the meeting package did not contain any efficacy or safety results. During the meeting, the applicant asked for clarification regarding their understanding that all commercial Humira® (adalimumab) is identical regardless of site of manufacture. The Agency clarified that US licensed Humira® and EU approved adalimumab are not necessarily considered identical and that a scientific bridge is needed. In the absence of a scientific bridge, the applicant inquired whether they could use data for the US licensed Humira® for subjects enrolled in the US and Canada to support comparison against guselkumab. The Agency noted that this may be acceptable, provided that the analysis is done for each trial separately and that there are sufficient numbers of subjects. As a post-meeting addendum, the Agency provided comments regarding establishment of a scientific bridge between US licensed Humira® and EU approved adalimumab.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission is adequate. The Division requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of domestic and international sites.

The sites which were selected for inspection had relatively high enrollment numbers (Dr. Tsen-Fang, Dr. Katarzyna), protocol violations (Dr. Bhutani, Dr. Katarzyna), discrepancies between the co-primary efficacy endpoints for the adalimumab arm (Dr. Bhutani) and lower than average response rates (IGA score of 0 or 1) for adalimumab (Dr. Katarzyna).

The Clinical Inspection Summary included the following results (Review by Roy Blay, Ph.D. dated 6/1/2017):

Table 2: Site Inspection Results

Site Number, Name, and Address	Protocol ID	# of Subjects	Classification	Inspection Dates
US93367 Bhutani Tina, MD The Regents of the University of California 185 Berry Street San Francisco, CA, 94107 USA	3001	14	NAI	April 4-6 2017
PL00239 Łoza Katarzyna Miedzyleski Szpital Specjalistyczny Ul Bursztynowa 2 Warszawa, 04-749 Poland	3002	19	(b) (5) Pending final classification	(b) (5)
TW00035 Tsai Tsen-Fang, M.D. National Taiwan University Hospital 7, Chung-Shan South Road, Taipei, 10002 Taiwan	3003	14	(b) (5) Pending final classification	(b) (5)

Source: Reviewer's Table

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Dr. Blay concluded that the conduct of the trials appears to be adequate and the data generated by these sites appears acceptable to support the use of this product for the proposed indication.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Guselkumab is a human IgG1λ monoclonal antibody produced in [redacted] (b) (4). Guselkumab targets the p19 protein subunit of extracellular human interleukin 23 (IL-23) and blocks the binding of IL-23 to the IL-23 receptor, leading to the reduction and/or inhibition of downstream production of IL-17A, a pro-inflammatory cytokine implicated in psoriasis pathogenesis. Guselkumab drug product is supplied at 100 mg/1.0 mL as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in pre-filled syringes (PFS) assembled into [redacted] (b) (4) passive needle guard.

The overall control strategy for guselkumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS) and drug product (DP) that have appropriate quality and are free of adventitious agents.

Summary of Quality Assessments

4.2.1. CQA Identification, Risk and Lifecycle Knowledge Management

Table 3 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

Table 3: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
IL-23 binding (potency)	Efficacy	Intrinsic to the molecule Impacted by oxidation, glycation, deamidation, aggregation and fragmentation. Decrease (b) (4) is expected during DP storage through expiry.	(b) (4)	Guselkumab does not bind to IL-23 that is already bound to IL-23 receptor and no CDC activity was detected using an in vitro cell based assay
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy, Pharmacokinetics and Safety/Immunogenicity Impacts IL-23 binding	Manufacturing process and exposure to heat, light and low and high pH stress. Minimal change is expected during (b) (4) DP storage through expiry.		N/A
Low Molecular Weight (LMW) Species (product-related impurities)	Efficacy and Pharmacokinetics	Manufacturing process and exposure to heat, light, and low and high pH stress. Minimal change is expected on stability.		N/A
Heavy chain (b) (4)	Efficacy	(b) (4) Minimal change is		N/A

Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
		expected on stability.	(b) (4)	
Heavy chain (b) (4)	Pharmacokinetics (FcRn binding)	Manufacturing process and exposure to acid treatment, light, heat, low and high pH stress. Minimal change is expected on stability.		N/A
Light chain (b) (4)	Efficacy	Manufacturing process and exposure to oxidative, light, heat, and high pH stress. Minimal change is expected on stability.		N/A
Light chain (b) (4)	Efficacy	Manufacturing process and exposure to light, heat, and high pH stress. Minimal change during storage is expected (b) (4) during DP storage through expiry.		N/A
Heavy chain (b) (4)	Efficacy	Manufacturing process and exposure to heat and high pH stress. Minimal change is expected on stability.		
Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
pH	Safety and Efficacy	Formulation process		N/A
Protein Content	Efficacy	Manufacturing process		N/A

Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
			(b) (4)	
Polysorbate 80 (PS 80)	Safety	Formulation		N/A

4.2.2. Drug Substance [guselkumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 4 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

Table 4: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A

			pg/mg).	
(b) (6) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (6)	(b) (4)	N/A
Residual (b) (4) (Process-related impurity)	Safety	(b) (4)		N/A
Culture Medium additives (b) (4) (Process-related impurity)	Safety	(b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		N/A
Leachables (Process-related impurity)	Safety	Process-related impurities potentially from manufacture		N/A

		and the DS container closure system (CCS)	(b) (4)	
Endotoxin	Safety and Purity	Raw materials or contamination during manufacturing		N/A
Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing		N/A

4.2.2.1. Description

Guselkumab is a recombinant, human IgG1λ monoclonal antibody and consists of two heavy chains that are each composed of 447 amino acids and two light chains that are each composed of 217 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 297 (Asn297). The molecular weight of deglycosylated guselkumab without C-terminal lysine is 144,258 Da.

The extinction coefficient was calculated and confirmed experimentally to be 1.70 mg^{-1} cm^{-1} mL at 280 nm. This value has been used during development and will continue to be used to determine the guselkumab protein concentration for commercial use.

4.2.2.2. Mechanism of Action

Guselkumab binds to the p19 subunit of human IL-23 and blocks the binding of IL-23 to the IL-23 receptor. IL-23 is produced by activated antigen presenting cells and binds to IL-23 receptor complexes expressed on NK cells and T cells. IL-23, alone or in combination with other cytokines (e.g., IL-1β), has been shown to promote the production of IL-17A, IL-17F, IL-6, and tumor necrosis factor α (TNFα), which are proinflammatory cytokines shown to contribute to inflammatory response in autoimmune disease such as psoriasis. Therefore, blocking the interaction between IL-23 and IL-23 receptor could reduce tissue inflammation and destruction in psoriasis patients.

4.2.2.3. Potency Assay

A cell-based bioassay that measures inhibition of IL-23 dependent receptor dimerization in modified human osteosarcoma U2OS cells (U2OS:IL23R cells) is used to control DS and DP potency. The U2OS:IL23R cells stably express modified versions of the IL-23 receptor subunits IL-23R and IL-12Rβ1, each of which expresses a segment of the β-galactosidase enzyme. The β-galactosidase enzyme is activated upon the dimerization of the IL-23 receptor subunits following treatment with IL-23, leading to the cleavage of a chemical substrate, which yields a luminescence signal. The activity of β-galactosidase is reduced when IL-23 receptor dimerization is blocked by guselkumab, leading to a reduction of the luminescence signal. The luminescence signal obtained from samples is plotted against guselkumab concentration and analyzed by a 4-parameter logistic model. The potency of test articles is calculated as a percentage relative to the reference material (RM).

4.2.2.4. Reference Material(s)

(b) (4)

4.2.2.5. Critical Starting Material or Intermediates

(b) (4)

4.2.2.6. Manufacturing Process Summary

(b) (4)

(b) (4)

4.2.2.7. Container Closure

(b) (4)

. The container closure system is suitable for guselkumab, based on stability data and maintenance of closure integrity.

4.2.2.8. Dating Period and Storage Conditions

The dating period for the (b) (4) and DS is (b) (4) and (b) (4) months, respectively, when stored at (b) (4) °C.

4.2.3. Drug Product [guselkumab] Quality Summary

Table 5 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that are derived from the drug product manufacturing process and general drug product attributes.

Table 5: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility	Safety and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure	(b) (4)	N/A
Endotoxin	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure		N/A
Container closure integrity	Safety	May be impacted by storage conditions		N/A
Color and turbidity of solution (general)	Safety and Efficacy	Formulation, contamination or degradation		N/A
Particulate Matter (translucent,	Safety/ Immunogenicity	Manufacturing process and CCS		N/A

visible and subvis ble) (Product or Process Related Impurities)			(b) (4)	
Polysorbate 80 concentration	Safety	Manufacturing process		N/A
Expelled Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Glidability (piston release and travel force)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS		Submission of additional leachable study data and a risk assessment will be addressed as a PMC

4.2.3.1. Potency and Strength

Guselkumab is supplied at 100 mg/1.0 mL syringe. Potency is defined as the percent activity relative to the current guselkumab reference standard. The potency assay is the same as described in the DS section of this memo.

4.2.3.2. Summary of Product Design

Guselkumab is supplied as a sterile, single-dose, preservative-free solution for SC injection in a pre-filled syringe that is assembled into (b) (4) passive needle guard. The drug product formulation consists of (b) (4) mM histidine, 0.05% (w/v) polysorbate 80, and (b) (4) % (w/v) sucrose, pH 5.8. The extractable volume is 1.0 mL.

4.2.3.3. List of Excipients

Excipients include (b) (4) mM histidine, 0.05% (w/v) polysorbate 80, and (b) (4) % (w/v) sucrose.

4.2.3.4. Reference material(s)

(b) (4)

4.2.3.5. Manufacturing Process Summary

(b) (4)

4.2.3.6. Container Closure

The primary container closure system for guselkumab DP consists of a 1-mL long syringe barrel (b) (4) with a 27-gauge

x1/2" (b) (4) fixed stainless steel needle, (b) (4) rigid needle shield (RNS), and a plunger stopper composed of (b) (4). Appropriate compatibility studies were performed for the container closure system.

The secondary container closure system consists of a tray insert, which is placed into a paperboard carton.

4.2.3.7. Dating Period and Storage Conditions

The dating period for guselkumab DP is 24 months when stored at 2-8ºC, protected from light.

4.2.4. Novel Approaches/Precedents:

None

4.2.4.1. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
Store in original carton until time of use.
Protect from light until use.
Do not freeze.
Do not shake.

4.2.4.2. Facilities

Guselkumab DS is manufactured at two facilities: (b) (4) Biogen Inc., Research Triangle Park, NC (FEI: 3000719749) and (b) (4) Janssen Sciences Ireland UC in Ringaskiddy, Cork County, Ireland (FEI: 3007029098). Cell banking operations occur at Janssen Biotech, Inc., Malvern PA (FEI: 3001610451).

A Pre-license Inspection was performed at Biogen Inc., 12/19/2016 – 12/23/2016. A three item Form FDA 483 was issued. The firm is acceptable. In addition, a Pre-license Inspection was performed at Janssen Sciences Ireland UC 2/27/2017 – 3/3/2017. A one item Form FDA 483 was issued. The firm is acceptable. The DS manufacturing and testing sites have been inspected multiple times within the recent past, demonstrating acceptable compliance.

The DP is manufactured and filled into the primary container closure at Cilag AG, Schaffhausen Switzerland (FEI: 3002806695). No inspections specific to guselkumab DP were conducted. The compliance status of the production and testing facilities associated with the manufacture of guselkumab DP is acceptable based on recent previous inspections and district recommendation. Secondary labeling and packaging is performed at Cilag AG, Schaffhausen Switzerland and AndersonBrecon, Inc., Rockford, IL, USA (FEI: 1421377). The compliance status of the secondary labelling and packaging facility and DP testing facilities are also acceptable.

4.2.5. Recommendation and Conclusion on Approvability

4.2.5.1. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761061 for guselkumab manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of guselkumab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

4.2.5.2. Approval Action Letter Language:

Under this license, you are approved to manufacture the [redacted] (b) (4) at Biogen Inc., Research Triangle Park, NC. You are approved to manufacture guselkumab drug substance at Janssen Sciences Ireland UC, Cork, Ireland. The 100 mg/1.0 mL drug product will be manufactured, assembled, labelled, and packaged at Cilag A.G., Schauffhausen, Switzerland. The 100 mg/1.0 mL drug product may also be packaged at AndersonBrecon, Inc., Rockford, IL.

The dating period for guselkumab drug product, 100 mg/1.0 mL, shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for guselkumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

The dating period for the [redacted] (b) (4) shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

4.2.5.3. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if Approvable:

PMC 1:
Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

PMC 2:
Provide additional data comparing the [redacted] (b) (4) Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the [redacted] (b) (4).

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

During the pivotal Phase 3 trials, guselkumab was supplied and administered via a single-dose, prefilled syringe (PFS) assembled with [redacted] (b) (4) Passive Needle Guard (PFS [redacted] (b) (4). This is the device with which guselkumab is to be marketed. The device was reviewed by Lieutenant Commander Keith Marin, MS, MBA; Center for Devices and Radiological Health, Office of Device Evaluation (CDRH/ODE). LCDR Marin concluded: "The sponsor has provided sufficient characterization of the device, functional performance testing, biocompatibility, sterility, shelf life, and shipping studies to support the safe and effective use of the device. As a result, CDRH/ODE recommends approval for the BLA for this combination product."

Carlos M Mena-Grillasca, RPh, Division of Medication Error Prevention and Analysis (DMEPA) provided a review of two Human Factors studies. The first study was a Summative Usability Study Report (October 2012) to validate the [redacted] (b) (4) (PFS) for a broad user base across two different drug viscosities. The user population included subjects with Rheumatoid Arthritis (RA), Psoriasis or Crohn's disease, caregivers, and Healthcare Providers (HCP). Use-related errors occurred among injection naïve participants and injection experienced participants (failure to pinch the skin and failure to active the safety mechanism). However, the evaluation of the risks associated with the use of the proposed product did not identify any new or unique risks. Therefore, Dr. Mena-Grillasca indicated that no action was needed to further mitigate the observed errors.

[redacted] (b) (4) The DMEPA reviewer concluded that the Human Factors validation study results were acceptable. Refer to the review by Carlos M Mena-Grillasca, RPh dated 5/15/2017).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) directed against the p19 subunit of interleukin 23 (IL-23). Binding of guselkumab to the p19 subunit of IL-23 disrupts the interaction of IL-23 with its cognate cell surface receptor, IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses, such as innate immune cell activation and CD4+ T-cell (e.g., Th17 cells) differentiation and activation. Guselkumab was shown to inhibit IL-23 mediated signaling and cytokine cascades by disrupting the interaction of IL-23 with its cognate cell surface receptor.

The applicant is seeking approval of guselkumab for the treatment of moderate to severe psoriasis. The maximum recommended human dose (MRHD) for guselkumab is 100 mg (1.67 mg/kg for a 60 kg individual) administered by subcutaneous injection at week 0, week 4 and every 8 weeks thereafter.

Guselkumab was shown to bind to human and cynomolgus IL-23 with high affinity with the equilibrium dissociation constant of 3.3 and 1.9 pM, respectively. Guselkumab bound to and inhibited IL-23 from a number of species, including guinea pig and non-human primate (baboon, chimpanzee, pigtail, and cynomolgus monkey), but not mouse or rat IL-23, and only partially inhibits dog IL-23. Guselkumab was shown to completely inhibit the activity of native guinea pig IL-23 and to have comparable reactivity to human and cynomolgus IL-23. Thus, cynomolgus monkeys and guinea pigs were selected as the pharmacologically relevant species for use in nonclinical studies with guselkumab.

Five-week subcutaneous (SC) and intravenous (IV) and 24-week SC toxicology studies were conducted in cynomolgus monkeys treated once weekly with guselkumab SC at doses of 10 or 50 mg/kg for 5 or 24 weeks or IV at a dose of 50 mg/kg for 5 weeks. No guselkumab-related effects on mortality, clinical signs, body weights, food consumption, physical or ophthalmic examinations, electrocardiograms (ECG), hematology, clinical chemistry, serum troponin, urinalysis, organ weights, and macroscopic or microscopic findings (including immunohistopathological T- and B-cell evaluation of the lymphoid tissues) were observed. There were no guselkumab-related alterations in T-cell dependent antibody response (TDAR) after 24 weeks of treatment. There were no neoplastic or test article-related non-neoplastic proliferative lesions. No target organs of toxicity were identified. The no observed adverse effect level (NOAEL) was 50 mg/kg/week for 5-week IV administration and for 24-week SC administration in cynomolgus monkeys based on the results in this study. After the 24th SC dose of 50 mg/kg/week, the C_{max} and AUC values were 993 µg/mL and 5,412 µg·day/mL, respectively. No antibodies to guselkumab were detected in animals during the dosing and recovery phases.

In an enhanced pre- and post-natal development (ePPND) study, pregnant cynomolgus monkeys (19, 20, and 20 in the 0, 10 and 50 mg/kg groups, respectively) were administered weekly SC doses of guselkumab up to 30 times the MRHD from the beginning of organogenesis to parturition. Neonatal monkey deaths occurred in the offspring of 1 of 16 control monkeys, 3 of 14 low dose monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and 3 of 14 monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). There were no other test article related effects

on maternal, fetal, or infant parameters during the study. There were no test article related effects on immune system parameters (lymphocyte phenotyping, serum immunoglobulin concentrations, TDAR, microscopic findings in lymphoid tissues). No other test article related macroscopic or microscopic findings were noted for the infants. After the 17th SC dose of 50 mg/kg/week on gestation day (GD) 133, the Cmax and AUC values were 733 µg/mL and 3930 µg.day/mL, respectively. Guselkumab concentrations in the infants on day 28 postpartum were similar to the ones in the maternal animals on postpartum day (PPD) 28. While serum guselkumab levels gradually decreased over time, they were still quantifiable for up to 91 days in most maternal and infant animals. Guselkumab exposure in infants was likely a result of transplacental distribution, as concentrations in milk samples were below the lowest quantifiable concentration for guselkumab. One of 40 maternal animals and one infant of 24 from the guselkumab treated groups had antidrug antibodies (ADA).

In a SC fertility study in young sexually mature female guinea pigs, no guselkumab-related changes in any of the evaluated fertility, early embryonic development and implantation parameters were observed at doses up to 100 mg/kg twice weekly (60 times the MRHD based on a mg/kg comparison). Two SC fertility studies were conducted in young sexually mature male guinea pigs. In the first male guinea pig fertility study, an increase in early resorptions per litter and the percentage of postimplantation loss was noted at the 100 mg/kg twice weekly dose. In the second male guinea pig fertility study, there were no treatment related effects noted at the 100 mg/kg twice weekly dose. The results of the second male guinea pig fertility study do not negate the results of the first male guinea pig fertility study. Therefore, no guselkumab-related changes in any of the evaluated fertility, early embryonic development and implantation parameters were observed at the lower dose of 25 mg/kg twice-weekly (15 times the MRHD based on a mg/kg comparison) for male guinea pigs.

No genetic toxicology or carcinogenicity studies have been conducted with guselkumab. The applicant provided an updated carcinogenicity risk assessment for guselkumab in this BLA submission. An analysis of published literature regarding the potential biological effects of IL-23 inhibition does not support a causal mechanistic/target-related link between IL-23 inhibition and increased cancer risk. No nonclinical studies to address the carcinogenic potential of guselkumab are recommended.

Guselkumab is approvable for the treatment of moderate to severe plaque psoriasis from a Pharmacology/Toxicology perspective. There are no recommended nonclinical PMCs/PMRs for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

IND 105004: Guselkumab indicated for moderate to severe plaque psoriasis.

The following pharmacology/toxicology studies were reviewed under IND 105004 except “SC Fertility and Early Embryonic Development Study in Male Guinea Pigs (Study # T-2014-021)” and “Enhanced Pre- and Post-natal Development Study in the Cynomolgus Monkey with a 6-Month Postnatal Evaluation (Study # 20029626)”. A summary of these studies is provided below. The code name for guselkumab is CNTO 1959.

5.3. Pharmacology

Primary pharmacology

Study 1 Binding of CNTO 1959 to Human IL-23 (Study # DIS.RES.DRR.023.me. doc, Non-GLP)

Guselkumab is a fully human IgG1λ mAb that is specific for the p19 subunit of IL-23. Guselkumab bound to human IL-23 in a dose-dependent manner. Guselkumab did not bind to the human IL-12/23p40 monomer, mouse IL-23, or human or mouse IL-12. Guselkumab was shown to bind to human and cynomolgus IL-23 with high affinity with the equilibrium dissociation constant of 3.3 and 1.9 pM, respectively. The results indicated that guselkumab bound to $_{74}$IHQGLIFYEK$_{83}$ of human IL-23p19.

Study 2 Mechanism of Action and Functional Effects of CNTO 1959-mediated Neutralization of Human IL-23 (Study # DIS.RES.DRR.024.me.doc, Non-GLP)

This in vitro study showed that guselkumab blocked IL-23/IL-23R binding with an IC_{50} of 0.06 nM against 170 pM IL-23. Guselkumab inhibited IL-23-induced phosphorylation of Signal Transducer and Activator of Transcription (STAT) 3 in a dose-dependent manner in NKL cells. Guselkumab also inhibited IL-23-induced cytokine production (IL-17A, IL- 17F, and IL-22) in mouse splenocytes and human peripheral blood mononuclear cells (PBMCs). The results indicated that guselkumab inhibited the binding of IL-23 to the IL-23 receptor and subsequent signaling events.

Study 3 Species Binding and Activity of CNTO 1959 (Study # DIS.RES.DRR. 025.me.doc, Non-GLP)

This in vitro study showed that guselkumab bound to and inhibited IL-23 from a number of species, including guinea pig and non-human primate (baboon, chimpanzee, pigtail, and cynomolgus monkey), but not mouse or rat IL23, and only partially inhibits dog IL-23. Guselkumab was shown to completely inhibit the activity of native guinea pig IL-23 and to have comparable reactivity to human and cynomolgus IL-23. Thus, cynomolgus monkey and guinea pig are pharmacologically relevant toxicology species for guselkumab.

Study 4 In Vivo Inhibition of Human IL-23-induced Cytokine Expression by CNTO 1959 in Mice (Study # DIS.RES.DRR.026.me.doc, Non-GLP)

Intraperitoneal administration of human or mouse IL-23 to C57BL/6 mice resulted in increased serum levels of several mouse cytokines and chemokines (e.g., IL-1α, G-CSF, IP-10, TNFα, GM-CSF, and MCP-1). Guselkumab significantly inhibited the increases of serum IL-1α and G-CSF induced by human IL-23 in C57BL/6 mice. Decreased MCP-1 levels after guselkumab treatment were also observed in C57BL/6 mice treated with human IL-23. Guselkumab was detected in the serum of mice intraperitoneally treated with guselkumab.

Secondary Pharmacology

Study 1 Assessment of CNT01959 Binding to Myosin Proteins in ELISA (Study # DIS.RES.DRR.027.gp.doc, Non-GLP)

This study investigated the potential cross-reactivity of guselkumab to myosin heavy chain protein in vitro, because a protein sequence alignment of human IL-23 and heart/muscle protein indicates that IL-23p19 and myosin (human and porcine) share a common stretch of 8 amino acids. The study showed that guselkumab bound to human IL-23 immobilized on plates and guselkumab did not bind to purified porcine or isolated recombinant human heavy chain myosin proteins immobilized on plates at concentrations up to 100 nM.

Safety Pharmacology

Study 1 IV Cardiovascular Study in Cynomolgus Monkeys (Study # T-2008-011, GLP)

A cardiovascular (CV) safety pharmacology study conducted in conscious cynomolgus monkeys that administered an IV dose of 10 or 50 mg/kg guselkumab identified a mild, non-adverse reduction in both heart rate (HR, 16 bpm or up to -9.9% vs vehicle) and body temperature (0.3°C or up to -0.8% vs vehicle {0.9% Sodium Chloride Injection}) after the administration of 50 mg/kg guselkumab. There were no adverse effects on ECGs and no treatment related effects on blood pressure in this study. Mean serum concentration of guselkumab at 24 hours postdose are 108 µg/mL for 10 mg/kg treated animals and 580 µg/mL for 50 mg/kg treated animals. The exposure to guselkumab at 50 mg/kg in this study is approximately 60 times the exposure clinically.

Safety pharmacology parameters, including CV, respiratory, and central nervous system assessments were also evaluated in the 5-week and 24-week toxicology studies in cynomolgus monkeys administered weekly IV or SC doses of up to 50 mg/kg. No treatment-related adverse effects were observed on any safety pharmacology parameters evaluated in this study.

5.4. ADME/PK

Absorption studies were conducted with guselkumab in separate pharmacokinetic (PK) studies in cynomolgus monkeys and toxicokinetic (TK) studies incorporated in toxicology studies in cynomolgus monkeys and guinea pigs. Standard distribution, metabolism, and excretion studies were not conducted with guselkumab because it is a monoclonal antibody. However, related distribution and excretion information obtained from the PK/TK studies are provided in the table below.

Table 6: Summary of PK Data

Type of Study	Major Findings
Absorption A single dose IV/SC PK study in cynomolgus monkeys, Study # CP2008T-051/CP2008T-050	Monkey $T_{1/2}$: SC: 10-11 days; IV: 12 days AUC_{inf}: 1 mg/kg IV: 130 µg·day/mL 1 mg/kg SC: 131 µg·day/mL

Type of Study	Major Findings
More data from TK studies are provided in other sections in this table.	5 mg/kg SC: 486 µg·day/mL *C_{max}:* 1 mg/kg IV: 21 µg/mL 1 mg/kg SC: 7 µg/mL 5 mg/kg SC: 34 µg/mL *CL or CL/F:* 1 mg/kg IV: 8 mL/kg/day 1 mg/kg SC: 8 mL/kg/day 5 mg/kg SC: 11 mL/kg/day *F:* 1 mg/kg: 101%, 5 mg/kg: 74%
Distribution A single dose IV/SC PK study in cynomolgus monkeys, Study # CP2008T-051/CP2008T-050 and A single dose IV/SC toxicology study in cynomolgus monkeys, Study # P-2007-255/CP2008T-034/ CP2008T-037 SC fertility and early embryonic development study in female guinea pigs, Study # T-2011-021 and CNTO 1959: enhanced pre and postnatal development study in the cynomolgus monkey with a 6-month postnatal evaluation, Study # 20029626	Following a single IV dose of 1 or 50 mg/kg guselkumab in monkeys, mean Vz values were 134 and 98 mL/kg, respectively. This suggests that guselkumab is mainly confined in the vascular space with limited extravascular tissue distribution, and that the distribution of guselkumab was generally dose independent. Following repeated SC administration to pregnant animals, guselkumab crossed the placenta into the developing fetus of both guinea pigs and cynomolgus monkeys, albeit to a much greater extent in monkeys (See Section 5.5.4 for details).
Excretion CNTO 1959: enhanced pre and postnatal development study in the cynomolgus monkey with a 6-month postnatal evaluation, Study # 20029626	On PPD 28, concentrations of guselkumab in milk samples were below the lowest quantifiable concentration for the assay (i.e., <0.02 µg/mL).
TK data from general toxicology studies A single dose IV/SC toxicology study in cynomolgus monkeys, Study # P-2007-255/CP2008T-034/CP2008T-037	<u>Single Dose Monkey</u> *$T_{1/2}$:* SC: 7-10 days; IV: 6 days *AUC_{inf}:* 50 mg/kg IV: 4267 µg·day/mL 1 mg/kg SC: 113 µg·day/mL 10 mg/kg SC: 614 µg·day/mL 50 mg/kg SC: 3358 µg·day/mL *C_{max}:* 50 mg/kg IV: 1364 µg/mL 1 mg/kg SC: 7 µg/mL 10 mg/kg SC: 49 µg/mL 50 mg/kg SC: 294 µg/mL *CL or CL/F:* 50 mg/kg IV: 12 mL/kg/day 1 mg/kg SC: 9 mL/kg/day 10 mg/kg SC: 17 mL/kg/day 50 mg/kg SC: 16 mL/kg/day

Type of Study	Major Findings
	F: 10 mg/kg: 72%, 50 mg/kg: 79% *Accumulation:* N/A *Dose proportionality:* Increased dose-proportionally from 10 to 50 mg/kg, but less than dose proportionally from 1 to 10 mg/kg. *ADA:* One 50 mg/kg IV animal that exhibited accelerated clearance in the terminal phase and a reduced $T_{½}$ for guselkumab.
3-week toxicity and tolerability study in male guinea pigs, Study # T-2009-024	<u>3-Week Male Guinea Pig</u> $T_{1/2}$: N/A *Accumulation:* moderate accumulation based on AUC following the last dose on Day 22 compared to AUC following the first dose on Day 1. *Dose proportionality:* Increased dose-proportionally
5-Week SC and IV and 24-Week SC Toxicity Studies in Cynomolgus Monkeys, Study # T-2008-007	<u>5-Week IV and SC Monkey</u> $T_{1/2}$: N/A *Accumulation:* Modest accumulation was observed, but steady state was not achieved following the fourth IV or SC administration on Day 21. *Dose proportionality:* Increased in an approximately dose-proportional manner over the dose range of 10 to 50 mg/kg after first and fourth dose. *Gender differences:* None *ADA:* None <u>24-Week SC Monkey</u> $T_{1/2}$: 10 mg/kg: 10 days 50 mg/kg: 9 days AUC_{inf} *(Day 162; M/F; Mean):* 10 mg/kg SC: 951 µg·day/mL 50 mg/kg SC: 5412 µg·day/mL C_{max} *(Day 162; M/F; Mean):* 10 mg/kg SC: 167 µg/mL 50 mg/kg SC: 993 µg/mL *Accumulation:* Steady state was achieved before the twelfth dose on Day 78. Moderate accumulation occurred following the weekly SC administration of guselkumab for 24 weeks. Steady state was achieved before the twelfth dose on

Type of Study	Major Findings
	Day 78. *Dose proportionality:* Increased in an approximately dose-proportional manner over the dose range of 10 to 50 mg/kg after first, twelfth and twenty-fourth doses. *Gender differences:* None *ADA:* None
TK data from reproductive toxicology studies SC fertility and early embryonic development study in female guinea pigs, Study # T-2011-021 SC fertility and early embryonic development study in male guinea pigs, Study # T-2011-031 CNTO 1959: enhanced pre and postnatal development study in the cynomolgus monkey with a 6-month postnatal evaluation, Study # 20029626	<u>Female Guinea Pig</u> *AUC (10th dose on Day 32)* 25 mg/kg: 327 µg·day/mL 100 mg/kg: 1273 µg·day/mL *C_{max} (10th dose on Day 32):* 25 mg/kg: 132 µg/mL 100 mg/kg: 510 µg/mL *ADA (Satellite animals, Day 32):* 25 mg/kg: 6/6 100 mg/kg: 6/6 *ADA (Main Study animals, G2D 30):* 25 mg/kg: Pregnant: 22/27 Pooled fetus: 1/16 100 mg/kg: Pregnant: 21/27 Pooled fetus: 5/16 <u>Male Guinea Pig</u> *AUC (19th dose on Day 64)* 25 mg/kg: 640 µg·day/mL 100 mg/kg: 2639 µg·day/mL *C_{max} (19th dose on Day 64):* 25 mg/kg: 243 µg/mL 100 mg/kg: 1004 µg/mL *ADA (Satellite animals, Day 32):* 25 mg/kg: 6/6 100 mg/kg: 6/6 *ADA (Main Study animals, G2D 30):* 25 mg/kg: Pregnant: 22/27 Pooled fetus: 1/16 100 mg/kg: Pregnant: 21/27 Pooled fetus: 5/16 See Section 5.5.4.

5.5. Toxicology

5.5.1. General Toxicology

Guselkumab demonstrated comparable species binding to IL-23 from humans, non-human primates (including cynomolgus monkeys), and guinea pigs, but only partial or no binding to dog, mouse, or rat IL-23. Thus, cynomolgus monkeys and guinea pigs were selected as the

pharmacologically relevant species for use in nonclinical studies with guselkumab. The applicant submitted one single dose and one pivotal 5-week (IV/SC)/24-week (SC) repeat dose toxicity studies in cynomolgus monkey and one 3-week SC toxicity and tolerability study in guinea pigs with guselkumab. A summary of these studies is provided below:

Study 1 Single Intravenous and Subcutaneous Dose Study in Cynomolgus Monkeys (Study # P-2007-255, Non-GLP)

In a single dose tolerability study in male cynomolgus monkeys, guselkumab was well tolerated at a single IV dose of 50 mg/kg or a single SC dose of 1, 10, or 50 mg/kg. Clinical findings were limited to fecal changes (soft and/or liquid feces) present in one animal each from the 10 mg/kg (SC) and 50 mg/kg (SC and IV) dose groups. There were no treatment-related effects on body weights.

Study 2 CNTO1959: A 5-Week Subcutaneous and Intravenous and 24-Week Subcutaneous Toxicity Study in Cynomolgus Monkeys with a 3-Month Recovery Period (Study # T-2008-007, GLP)

Five-week SC and IV and 24-week SC toxicology studies were conducted in young adult to adult cynomolgus monkeys administered guselkumab SC at doses of 10 or 50 mg/kg, once per week for 5 or 24 weeks or IV at a dose of 50 mg/kg for 5 weeks. The vehicle used in this study was 0.9% Sodium Chloride Injection. No guselkumab-related effects on mortality, clinical signs, body weights, food consumption, physical or ophthalmic examinations, ECG, hematology, clinical chemistry, serum troponin, urinalysis, organ weights, and macroscopic or microscopic findings (including immunohistopathological T- and B-cell evaluation of the lymphoid tissues) were observed. There were no guselkumab-related alterations in TDAR after 24 week treatment. No target organs of toxicity were identified. There were no neoplastic or test article-related non-neoplastic proliferative lesions in this study. The NOAEL was 50 mg/kg/week for 5-week IV administration and for 24-week SC administration in cynomolgus monkeys based on the results in this study. After the 24th SC dose of 50 mg/kg/week, the C_{max} and AUC values were 993 µg/mL and 5,412 µg·day/mL, respectively. No antibodies to guselkumab were detected in animals during the dosing or recovery phases.

Study 3 3-Week SC Tolerability Study in Male Guinea Pigs (Study # T-2009-024, Non-GLP)

In a 3-week tolerability study in male guinea pigs that was designed to provide guidance regarding the suitability of the guinea pig in assessing male and female fertility, guselkumab was administered SC at doses of 0, 10, 50, and 100 mg/kg twice-weekly. The vehicle used in this study was 0.9% Sodium Chloride Injection. There were no guselkumab-related effects on mortality, clinical signs, gross lesions, body weights or body weight gains. The C_{max} and AUC increased in an approximately dose-proportional manner and moderate drug accumulation in the systemic exposure levels occurred following twice weekly subcutaneous treatment of guselkumab for 3 weeks in Hartley guinea pigs. Based on these findings, the guinea pig was selected as an appropriate species for use in subsequent fertility studies.

5.5.2. Genetic Toxicology

Genetic toxicology studies are not applicable to mAbs and were not conducted with guselkumab based on ICH S6R1 guidance, Guidance for Industry – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

5.5.3. Carcinogenicity

Guselkumab cannot be tested in a traditional 2-year rodent study to evaluate its carcinogenic potential due to its species specific binding in monkeys and/or guinea pigs. It is unlikely that a carcinogenicity study with long term antagonism of IL23p19 in rodents would be very informative.

The applicant provided an updated carcinogenicity risk assessment for guselkumab in this BLA submission. No significant changes have been made to the original carcinogenicity risk assessment for guselkumab that was submitted to the FDA on November 25, 2013.

This carcinogenicity risk assessment includes a literature evaluation of the potential role of the IL-23 pathways in tumor development and anti-tumor immunity. This evaluation together with an evaluation of data from the repeat-dose toxicology study in cynomolgus monkeys, form the basis of this assessment for guselkumab. A brief summary is provided below.

Published literature is mixed on potential effects on malignancy risk from the inhibition of IL-23 activity. Exogenously administered or overexpressed IL-23 has demonstrated antitumor properties in a variety of mouse models. However, treatment with anti-mouse-IL-23 antibodies has shown an antitumor activity in endogenous host defense against neoplasia in other mice studies. Mice genetically manipulated to be deficient in IL-23 (IL-23p19$^{-/-}$) were resistant to chemically induced tumor formation and metastases in some mouse models.

In general, immunosuppressive drugs tend to be associated with increased cancer risk or increased infection. The immune function tests in the repeat dose monkey toxicity study showed that guselkumab did not cause immunosuppression or deplete T-cells. No histopathological evidence of pre-neoplastic changes were observed in organs or tissues examined following SC administration of guselkumab to monkeys at dose levels up to 50 mg/kg once weekly for 24 weeks followed by a 3-month post-dose observation period.

Analysis of published literature regarding the potential biological effects of IL-23 inhibition together with an evaluation of data from the repeat-dose toxicology study in cynomolgus monkeys does not support a causal mechanistic/target-related link between IL-23 inhibition and increased cancer risk. No additional nonclinical studies are recommended to evaluate the carcinogenic potential of guselkumab from a Pharmacology/Toxicology perspective.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The potential effects of guselkumab on fertility and early embryonic development were evaluated in separate studies in male and female guinea pigs. The first two SC fertility studies in guinea pigs with guselkumab were reviewed under IND 105004. A summary of these studies is

provided below. G1D X is equivalent to Gestation Day X of the 1st pregnancy, G2D X is equivalent to Gestation Day X of the 2nd pregnancy.

Note: Presumed pregnant female guinea pigs were utilized for the female and male fertility studies because this facilitates synchronization of mating and gestation, delivery, and postpartum estrus/mating. This was especially important given the length (approximately 18 days) and the unpredictability of the estrous cycle in the guinea pig as compared to the estrous cycle of the mouse and rat which is easier to determine and substantially shorter. Additionally, pregnancy rates in the guinea pig are notably much higher when pregnant guinea pigs are allowed to mate just following delivery (postpartum mating).

Study 1 SC Fertility and Early Embryonic Development Study in Female Guinea Pigs (Study # T-2011-021, GLP)

In this female fertility study, three groups of 30 pregnant female guinea pigs received 0, 25, or 100 mg/kg guselkumab SC twice weekly for a total 10 doses, starting on G1D 44, approximately 3 weeks prior to the estimated G2D 0 (i.e., day of natural delivery and postpartum mating) and continued through G2D 7. The vehicle used in this study was 0.9% Sodium Chloride Injection. Two presumed pregnant females were co-housed with each male to allow for mating on the day that natural delivery occurred (i.e., day of postpartum estrus). Male guinea pigs were used only as breeders. Females that did not naturally deliver a litter were euthanized on G1D 78, and females that delivered a litter were euthanized on G2D 30.

There were no treatment-related effects on mortality, clinical observations, gross lesions at necropsy, and fertility parameters, except that body weight gains were slightly reduced at 100 mg/kg prior to and after parturition. The fertility NOAEL in female guinea pigs was 100 mg/kg (200 mg/kg/week).

Study 2 SC Fertility and Early Embryonic Development Study in Male Guinea Pigs (Study # T-2011-031, GLP)

A male fertility study was conducted in Dunkin Hartley guinea pigs. Three groups of 25 male guinea pigs received 0, 25, or 100 mg/kg guselkumab subcutaneously twice weekly for a total of 21 doses, beginning approximately 7 weeks prior to the estimated day of mating. The vehicle used in this study was 0.9% Sodium Chloride Injection. One untreated, presumed pregnant female was co-housed with each male to allow for mating on the day that natural delivery occurred (i.e., day of postpartum estrus). Females were monitored to G2D 30 (Gestation Day 30 of the 2nd pregnancy), after which they were necropsied and the uterine contents examined. Treated males were sacrificed on Day 72 (24 hr after the last dose) and sperm motility and sperm concentration were evaluated.

There were no treatment-related effects on mortality, clinical observations, body weights, food consumption, macroscopic or microscopic findings in the treated males. All male reproductive organ weights and sperm parameters (motility and concentration) were comparable between the 3 dose groups. There were no treatment-related effects on mating or fertility at any dose. Pregnancy occurred in 22 (91.7%), 19 (90.5%) and 22 (95.6%) guinea pigs in the 0, 25, and 100 mg/kg twice weekly dose groups, respectively. There were no treatment-related effects on the numbers of corpora lutea, implantations, and percent pre-implantation loss, litter sizes, live and dead fetuses, and late resorptions as determined on G2D 30. However, five untreated sows mated to males in the 100 mg/kg twice weekly dose group had 100% early resorbed litters. As a

result, the average number of early resorptions per litter and the percentage of postimplantation loss were increased in the 100 mg/kg twice weekly dose group compared to controls.

It appears that these effects were treatment related and may be due to lower sperm motility, lower sperm count, and/or lower sperm density in 5 high dose males. The applicant was asked to provide the historical control ranges for these parameters in male guinea pigs and provide a more detailed rationale to support that these effects are not treatment related. The reproductive NOAEL in male guinea pigs was considered to be 25 mg/kg twice weekly based on the results from this study.

The applicant stated that **"**no additional historical control data is available at the Test Facility beyond this particular male fertility study in guinea pigs and validation datasets" and provided a rationale that concluded "In the male fertility study, the cause and toxicological significance for the increase in the number of untreated female guinea pigs with all early resorptions (5 out of 22) at the high dose only, 100 mg/kg twice-weekly, could not be determined; however, the overall weight of evidence indicates that the increased post-implantation loss observed at 100 mg/kg (twice-weekly) is not treatment-related based on the following:

1) In the males treated with guselkumab twice-weekly at 25 mg/kg or 100 mg/kg, including the 5 males that mated with females that had all early resorptions at cesarean sectioning, no differences were noted between the drug-treated and control groups for sperm motility, sperm count, and/or sperm density, and there were no differences between drug-treated and control males for reproductive organ weights;

2) Comparable pre-implantation loss was observed between controls and guselkumab-treated females;

3) No effect on implantation (fertility) in untreated females was observed as evidenced by comparable numbers of implantations in the guselkumab-treated groups compared with controls;

4) For untreated females with live fetuses at cesarean sectioning, no effect was observed for the number of live fetuses, dead fetuses, early resorptions, or late resorptions (T-2011-021);

5) In the female fertility study, there was no effect on the fertility of females that were directly dosed with guselkumab (T-2011-021), including pre- or post-implantation loss, or numbers of live and dead fetuses; and

6) In the Non-GLP male fertility study, two untreated females, one of six (16.6%) from the control group and one of eight females (12.5%) from the 50 mg/kg group exhibited all resorptions.

Importantly, safety margins in the male fertility study at the high dose (100 mg/kg, twice-weekly) are 209X based on C_{max}, and 24X based on AUC when compared to a single 100 mg dose administered subcutaneously during the Phase 1 clinical trial (CNTO1959PSO1001). At the low dose (25 mg/kg, twice-weekly), safety margins are 51X based on C_{max}, and 6X based on AUC when compared to a single 100 mg dose administered subcutaneously during Phase 1b of clinical trial CNTO1959PSO1001. While the toxicological significance, if any, of the increased post-implantation loss that occurred at 100 mg/kg could not be determined, it is the position of

Janssen R&D that a significant, and potentially highly underestimated, safety margin exists at the low dose where no similar effect was observed."

However, this reviewer determined that the increased post-implantation loss that occurred at 100 mg/kg twice weekly could not be ruled out as treatment related and the fertility NOAEL in male guinea pigs is 25 mg/kg twice weekly based on the results from this study and review of the additional information the applicant provided.

Subsequently, the applicant submitted a second GLP male fertility and early embryonic development study in Dunkin Hartley guinea pigs (Study #: T-2014-021) and a Non-GLP mechanistic study of guselkumab by subcutaneous injection in the male Dunkin Hartley guinea pigs (Study #: T-2014-022). The mechanistic study is a Non-GLP study with fewer animals compared to the second male fertility study. Therefore, the Non-GLP mechanistic study is not reviewed for this BLA. However, the second male fertility study in guinea pigs is reviewed below.

Study 3 SC Fertility and Early Embryonic Development Study in Male Guinea Pigs (Study # T-2014-021, GLP)

A second GLP male fertility and early embryonic development study was conducted in Dunkin Hartley guinea pigs as a result of findings noted in study T-2011-031, in which an increased number of resorptions (100%) was noted in untreated females mated to males administered twice-weekly SC doses of 100 mg/kg guselkumab. The study was designed to evaluate the reproducibility of the finding, and to provide a more detailed rationale to support the applicant's conclusion that the increase in postimplantation loss observed in Study T-2011-031 was not treatment related.

The study design was similar to the previously conducted male fertility study. Males (25/group) were administered twice-weekly SC doses of either the control article (0.9% sodium chloride, USP, given to 2 control groups), or 100 mg/kg guselkumab. Dosing initiated approximately 7 weeks prior to the estimated day of postpartum mating, and continuing until 21 doses were administered, with the last dose being administered on Day 71. The control article and guselkumab were administered SC to the shaved back at a dose volume of 2 mL/kg. Injection sites were rotated between four treatment sites on the back. A group of satellite TK/ADA males (6/group) also received twice weekly doses of the control article or 100 mg/kg guselkumab by the same route and regimen, until a total of 20 doses were administered, with the last dose administered on Day 67. One untreated, presumed pregnant female was co-housed with each male to allow for mating on the day that natural delivery occurred (i.e., day of postpartum estrus). Females were monitored to G2D 30 (Gestation Day 30 of the 2nd pregnancy), after which they were necropsied and the uterine contents examined. Treated males were sacrificed on Day 72 (24 hr after the last dose) and sperm motility and sperm concentration were evaluated.

Guselkumab was well tolerated in male guinea pigs when administered SC twice weekly at a dose level of 100 mg/kg. No guselkumab related effects on male reproductive tissues, sperm parameters, or fertility and early embryonic development were observed in this study. This study did not replicate the increase in the number of untreated females with all early resorptions observed in the previous study (Study # T-2011-031). The paternal reproductive (mating, fertility, and embryo-fetal survival) NOAEL for guselkumab is 100 mg/kg administered twice weekly in guinea pig based on the results from this study. After the 19th SC dose of 100 mg/kg

twice weekly (Day 64), the C_{max} and AUC values were 1009 µg/mL and 2734 µg·day/mL, respectively. See the following table for the details. Antibodies to guselkumab were detected in 5 of 6 (83.3%) guselkumab-dosed satellite TK male guinea pigs. Although all guselkumab-treated males from the main study were negative for ADA, residual serum guselkumab concentrations may have interfered with the detection of the presence of anti-guselkumab antibodies in the assay.

However, the results from this male fertility study do not negate the results from the previous male fertility study. Therefore, the labeling for guselkumab for impairment of male fertility will be based a fertility NOAEL of 25 mg/kg twice weekly derived from the first male fertility study.

Table 7: Summary of Mean Exposure Data

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 (ie, 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 (ie, the 13th dose) or $AUC_{Day\ 64-67}$ following the dose on Day 67 (ie, the 20th dose) by $AUC_{Day\ 1-4}$ following the first dose on Day 1, respectively.

Source: Table 8 from Toxicology Written Summary submitted by the applicant.

Embryo-Fetal Development

A standalone EFD study was not conducted for guselkumab. Instead, an ePPND study was conducted in monkeys with guselkumab.

Prenatal and Postnatal Development

Study title/ number: CNTO 1959: Enhanced Pre and Postnatal Development Study in the Cynomolgus Monkey with a 6-Month Postnatal Evaluation/ 20029626

Key Study Findings

In an ePPND study, pregnant cynomolgus monkeys (19, 20, and 20 in the 0, 10 and 50 mg/kg groups, respectively) were administered weekly SC doses of guselkumab up to 30 times the

MRHD from the beginning of organogenesis to parturition. Neonatal monkey deaths occurred in the offspring of 1 of 16 control monkeys, 3 of 14 low dose monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD on a mg/kg basis) and 3 of 14 monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD on a mg/kg basis). There were no other test article related effects on maternal, fetal, or infant parameters during the study. There were no test article related effects on immune system parameters (lymphocyte phenotyping, serum immunoglobulin concentrations, TDAR, microscopic findings in lymphoid tissues). No other test article related macroscopic or microscopic findings were noted for the infants.
After the 17th SC dose of 50 mg/kg/week on GD133, the C_{max} and AUC values were 733 µg/mL and 3930 µg·day/mL, respectively. Guselkumab concentrations in the infants on BD 28 were similar to the ones in the maternal animals on PPD 28. While serum guselkumab levels gradually decreased over time, they were still quantifiable for up to 91 days in most maternal and infant animals. Guselkumab exposure in infants was likely a result of transplacental distribution, as milk samples were below the lowest quantifiable concentration for guselkumab. One of 40 maternal animals and one infant out of 24 from the guselkumab treated groups were ADA positive.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 10 and 50 mg/kg/week, once weekly from gestation day (GD) 20-22 until parturition (approximately GD 160 ± 10) for a total of approximately 21 doses/animal
Route of administration:	SC Injection
Formulation/Vehicle:	0.9% Sodium Chloride for Injection, USP
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	20 mated females/group (19 for control group)
Satellite groups:	N/A
Study design:	Pregnancy was determined by ultrasound monitoring and confirmed by monkey chorionic gonadotropin (mCG) test when necessary. During gestation, the adult females were monitored for clinical signs (twice daily) and changes in food consumption (once daily), body weight (at enrollment, GD25 and weekly thereafter until delivery), and pregnancy status including embryo-fetal development status (via ultrasound) (biweekly for general conditions, monthly for developmental landmarks). Blood samples from the adult females were collected at various time points throughout the study for clinical pathology, lymphocyte subset evaluation (flow cytometry), toxicokinetic (TK, including milk) and ADA analyses. The pregnant females were allowed to deliver their

	infants by natural birth. For approximately 6 months postpartum/postnatal, the adult females and infants were evaluated for changes in clinical signs, body weight, and/or other parameters. Infants underwent neurobehavioral assessments and skeletal evaluation within the first month. Blood samples from the infants were collected at various time points throughout the study for toxicokinetics and ADA formation analyses. Postnatal immunological assessments were conducted, including T-cell dependent antibody response to KLH and lymphocyte subset evaluation (flow cytometry). The infants were euthanized on approximately BD 185±3. An external and visceral exam and full necropsy were conducted on all infants, including macroscopic tissue examinations. A subset of tissues were collected, weighed, and preserved, and selected tissues were evaluated for histopathology (including immunohistochemistry of lymphoid tissues). Infants were maintained with their mothers for the entire postnatal period, and the mothers were released from the study once their infant was no longer on study.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

F_0 Dams

Survival:	No test article related effects on survival were noted.
Clinical signs:	No test article related clinical findings were noted.
Body weight:	No test article related effects on body weight were observed.
Feed consumption:	No test article related effects on feed consumption were observed.
Uterine content and reproductive parameters:	A total of sixteen Group 1 (control), fourteen Group 2 (10 mg/kg/week), and fourteen Group 3 (50 mg/kg/week) infants were delivered by natural birth. There were no guselkumab-related effects on gestation length or pregnancy/postpartum outcomes that were considered related to maternal administration of guselkumab. Overall fetal loss (abortion) was 3 of 19 (15.8%) in the control group and 6 of 20 (30.0%) in both the 10 and 50 mg/kg/week guselkumab groups. The numerical differences in fetal loss between treated groups and controls were not able to be ruled as unrelated to

	guselkumab administration even though the fetal loss in the guselkumab groups was not dose related and was within historical ranges for the Testing Facility (both overall and per trimester). There were no other guselkumab-related maternal or fetal observations associated with the abortions, including placenta, fetal measurements and fetal external, visceral, skeletal, and/or heart evaluations.
Necropsy observation:	No test article related effects were noted.
Toxicokinetics and ADA:	The pregnant monkeys in Group 2 and Group 3 were exposed to guselkumab continuously from GD20 through the whole pregnancy period until parturition. The C_{max} 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 GD 91 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 animals. The mean $T_{1/2}$ of guselkumab was relatively consistent between the 10 and 50 mg/kg/week dose groups in maternal animals. Guselkumab concentrations were below the lowest quantifiable concentration in the milk samples on PPD 28 while significant guselkumab concentrations (11 and 74 µg/mL for the 10 and 50 mg/kg dose groups, respectively) were observed in the serum samples at the same time point. This suggested that no guselkumab reached the mammary glands to be secreted into the milk and also indicated that the drug in the infants was mainly from transplacental distribution. The presence of neutralizing antibodies was not assessed in the milk samples. One of 40 maternal animals from the guselkumab treated groups was ADA positive. The animal exhibited an accelerated decrease in guselkumab concentrations starting from the measurement on GD 56.
Other:	There were no test article related changes in hematology, coagulation, clinical chemistry, and immune system parameters (lymphocyte phenotyping, serum immunoglobulin concentrations, TDAR, microscopic findings in lymphoid tissues) in any dose group when compared to the control group.

Table 8: Summary of Mean PK Data

Summary of Mean TK Parameters

Group	Maternal PK Following the Dose on GD20			Maternal PK Following the Dose on GD133				Maternal PP[b]	Infant
	C_{max} (µg/mL)	T_{max}[a] (day)	$AUC_{GD20-27}$ (µg·day/mL)	C_{max} (µg/mL)	T_{max}[a] (day)	$AUC_{GD133-140}$ (µg·day/mL)	R	$T_{1/2}$ (day)	$T_{1/2}$ (day)
10 mg/kg/week	83.00	3.00	464.06	152.67	1.00	895.69	2.05	9.38	11.57
50 mg/kg/week	368.70	3.00	2068.95	732.95	3.00	3930.06	1.98	10.21	13.61

[a] Median, instead of Mean, was presented for T_{max}, which is the time elapsed from the dose on GD20 or GD133.
[b] Maternal animals - Postpartum

Source: Text Table 23 from study report T-2012-019/20029626 for "CNTO 1959: Enhanced Pre and Postnatal Development Study in the Cynomolgus Monkey with a 6-Month Postnatal Evaluation".

F_1 Generation

Survival: The number of surviving infants per group was 15, 11, and 11 in the control, 10 mg/kg/week, and 50 mg/kg/week groups, respectively. Seven infants died or were euthanized within 35 days postnatal. The specific cause for each death could not be determined. The overall incidence of infant loss (1 of 16, or 6.3% for the control group and 3 of 14, or 21.4% for each of the guselkumab groups) appears treatment related even though the mid and high dose animals had a similar response

Clinical signs: No test article related clinical findings were noted.

Body weight: No test article related effects on body weight were observed.

Feed consumption: No test article related effects on feed consumption were observed.

Physical development: No test article related effects on physical development were observed.

Neurological assessment: No test article related effects on neurological assessment were observed.

Toxicokinetics and ADA: Quantifiable concentrations were observed up to 91 days post parturition for most infant animals. The mean $T_{1/2}$ of guselkumab was relatively consistent between the 10 and 50 mg/kg/week dose groups in infant animals and slightly longer than in the maternal animals. Guselkumab concentrations in the infants were similar to the ones in the maternal animals on PPD 28. The ratio of infant to maternal serum concentration at the time point of 28 days post-delivery was approximately 0.70 and 0.83 for the 10 mg/kg and 50 mg/kg dose group, respectively. See the following table for the details.

One infant out of 24 from the guselkumab treated groups was ADA positive. Serum guselkumab concentrations in all collected samples from the infant were below the lowest quantifiable concentration.

Two control infants were ADA positive for unknown

reasons; both maternal females were negative for ADA.

Other: There were no test article related changes in hematology, coagulation, clinical chemistry, and immune system parameters (lymphocyte phenotyping, serum immunoglobulin concentrations, TDAR, microscopic findings in lymphoid tissues) in any dose groups when compared to the control group.

Table 9: Summary of Mean Exposure Data in Monkey ePPND Study

Summary of Mean Exposure (C_{max} and AUC [SD]) of Guselkumab Following Weekly SC Administration of Guselkumab in Cynomoglus Monkeys in an Enhanced Prenatal/Postnatal Development GLP Study with a 6-Month Postnatal Evaluation (T-2012-019)

TK Parameters	10 mg/kg	50 mg/kg
Adult Females[a]		
1st Dose on GD 20:		
C_{max} (µg/mL)	83.00 (34.34)[b]	368.70 (97.81)
$AUC_{GD\ 20\text{-}27}$ (µg·day/mL)	464.06 (163.16)[b]	2068.95 (473.51)
17th Dose on GD 133:		
C_{max} (µg/mL)	152.67 (30.89)[c]	732.95 (257.51)[d]
$AUC_{GD\ 133\text{-}140}$ (µg·day/mL)	895.69 (130.98)[c]	3930.06 (1385.36)[d]
R[e]	2.05 (0.93)[f]	1.98 (0.55)[g]
Mean Serum Concentration on PPD 28 (µg/mL)	11.34 (5.26)[h,i]	73.55 (48.35)[i]
Milk Samples on PPD 28	<LLOQ	<LLOQ
Infants[i]		
Mean Serum Concentration on BD 28 (µg/mL)	7.96 (4.17)[j,k]	61.18 (33.20)[j,k]

[a] Pregnant females (20/group) were dosed approximately once a week from GD 20-22 until parturition (approximately GD 160 ± 10 days), for a total of approximately 21 doses.
[b] N=19 (data for 1 animal was noted as NR).
[c] N=15 (data for 5 animals were noted as NS).
[d] N=16 (data for 4 animals were noted as NS).
[e] The accumulation ratio (R) was calculated by dividing $AUC_{GD\ 133\text{-}140}$ following the dose on GD 133 (ie, the 17th dose) by $AUC_{GD\ 20\text{-}27}$ following the dose on GD 20.
[f] N=14 (data for 1 animal was noted as NR, and data for 5 animals were noted as NS).
[g] N=16 (data for 4 animals were noted as NS).
[h] N=11 for both the 10 and 50 mg/kg groups; (data for 9 animals [in each group] were noted as NS).
[i] 14 infants born/group: 11 males and 3 females in the 10 mg/kg group, 9 males and 5 females in the 50 mg/kg group.
[j] N=11 (data for 9 animals were noted as NS).
[k] Guselkumab concentrations in the infants were similar to the ones in the maternal animals on PPD 28.

Source: Table 10 from Toxicology Written Summary submitted by the applicant.

F2 Generation: Not evaluated.

5.5.5. Other Toxicology Studies

Study 1 Cross-Reactivity Study of Biotinylated CNTO 1959 with Human and Cynomolgus Monkey Tissue (Study # T-2007-007, Non-GLP)

Biotinylated form of guselkumab at concentrations of 2 and 50 µg/mL was applied to cryosections of normal human and cynomolgus monkey tissues (1 donor/tissue) to evaluate the potential cross-reactivity of guselkumab. Weak to strong guselkumab -Bio staining of rare to occasional human IL-23 expressing cells was noted at 50 µg/mL, but not at 2 µg/mL. There was no staining by the negative control antibody or in assay control slides. In general, the

cynomolgus monkey tissue staining patterns were similar to those seen in the human. It was unexpected that the most prominent staining was observed in the cytoplasm of striated myocytes in skeletal and cardiac muscle in both monkey and human tissue.

Study 2 Cross-Reactivity Study of Biotinylated CNTO 1959 with Human and Cynomolgus Monkey Tissue (Study # T-2008-009, GLP)

Guselkumab at concentrations of 2 and 50 µg/mL was applied to cryosections of normal human and cynomolgus monkey tissues (3 human donors per tissue and 1 cynomolgus monkey donor per tissue, where available) to evaluate the potential cross-reactivity of guselkumab. Guselkumab produced moderate to intense staining of the positive control (human IL-23 UVresin spot slides). There was no staining by the negative control antibody or in assay control slides. In general, the cynomolgus monkey tissue staining patterns were similar to those seen in the human with only minor differences observed.

In human tissues, guselkumab stained the following tissue elements and subcellular or extracellular locations: Striated (skeletal) myocytes in skeletal muscle, esophagus, eye and prostate - cytoplasm (particularly peripheral cytoplasm); Striated (cardiac) myocytes in heart, cytoplasm; Macrophages and/or dendritic cells in multiple human tissues (membrane, cytoplasm, and cytoplasmic granules); decidual stromal cells in placenta; Epithelial cells in a few tissues (adrenal, breast, lung, Fallopian tube, urinary bladder [cytoplasm, cytoplasmic granules and/or ring structures]); Intravascular/extracellular proteinic material in a few tissues. Questionable staining also was observed in glial cells and gray matter neuropil (cytoplasm) in brain and spinal cord and glomerular tuft cells (cytoplasm) in kidney.

In cynomolgus monkey tissues, guselkumab stained the following tissue elements and subcellular or extracellular locations: Striated (skeletal) myocytes in skeletal muscle, eye, esophagus, peripheral nerve, thymus, and prostate – cytoplasm (particularly peripheral cytoplasm); Striated (cardiac) myocytes in heart, cytoplasm; Macrophages and/or dendritic cells in multiple monkey tissues (membrane, cytoplasm, and cytoplasmic granules); decidual stromal cells in placenta; Epithelial cells in a few tissues (adrenal, pituitary, skin, Fallopian tube, thyroid, urinary bladder, uterus-cervix [cytoplasm, cytoplasmic granules and/or ring structures]); Intravascular/extracellular proteinic material in a few tissues. Questionable staining also was observed in glial cells and gray matter neuropil (cytoplasm) in brain and spinal cord.

Study 3 Cross-Reactivity Study of CNTO1959 with Select Normal Cynomolgus Monkey Tissues Using a Human Test Article Detection Reagent (Monkey-Adsorbed Anti-Human IgG Secondary Antibody) (Study # T-2009-003, Non-GLP)

Guselkumab at concentrations of 50, 10, and 2 µg/mL was applied to cryosections of normal cynomolgus monkey heart, striated (skeletal) muscle, and thyroid (1 donor per tissue).

Guselkumab stained the following tissue elements and subcellular or extracellular locations: striated (cardiac) myocytes in heart (cytoplasm), striated (skeletal) myocytes in skeletal muscle (cytoplasm, particularly peripheral cytoplasm), macrophages and/or dendritic cells in spleen with lesser staining by negative control antibody, and follicular epithelium and colloid in thyroid. Guselkumab produced strong to intense staining of the positive control (human IL-23 UV-resin spot slides), but did not specifically react with the negative control (PTHrP 1-34 UV-resin spot slides). The negative control antibody, HuIgG1, did not specifically react with either the positive

or negative control. There also was no staining of the assay control slides. In addition, weak to strong staining with guselkumab of rare to occasional human IL-23-expressing cells was evident at 50 and 10 µg/mL, but staining was greatly reduced at 2 µg/mL. There was no staining in human IL-23-expressing cells with the negative control antibody or in assay control slides.

The in vitro patterns of guselkumab in the present study were comparable to the in vitro patterns of biotinylated guselkumab in prior human and monkey cross-reactivity study (T-2008-009).

Study 4 Hemolytic Potential of CNTO 1959 (Lot Number R06K013) with Human Whole Blood (Study # P-2007-157, Non-GLP)

Blood samples were collected from normal human volunteers and co-incubated with guselkumab in 5% dextrose at concentrations up to 21 mg/mL for 40 minutes at 37 °C. No hemolysis was noted in this study.

Study 5 Hemolytic Potential of CNTO 1959 (Lot Number 11562:180) with Human Whole Blood (Study # P-2008-048, Non-GLP)

Blood samples were collected from normal human volunteers and co-incubated with guselkumab in 5% dextrose at concentrations up to 65 mg/mL for 40 minutes at 37 °C. No hemolysis was noted in this study.

Study 6 Compatibility Testing of CNTO 1959 (Lot Number R06K013) with Human Serum (Study # P-2007-158, Non-GLP)

Blood samples were collected from normal human volunteers and spun down for serum. Serum was then co-incubated with guselkumab in 5% dextrose at concentrations up to 21 mg/mL for 25 minutes at room temperature. No precipitation was noted in this study.

Study 7 Compatibility Testing of CNTO 1959 (Lot Number 11562:180) with Human Serum (Study # P-2008-047, Non-GLP)

Blood samples were collected from normal human volunteers and spun down for serum. Serum was then co-incubated with guselkumab in 5% dextrose at concentrations up to 65 mg/mL for 25 minutes at room temperature. No precipitation was noted in this study.

Juvenile Animal Toxicology Studies:
No juvenile animal toxicology studies were conducted with guselkumab. A study conducted in cynomolgus monkeys to assess the effects of guselkumab on pre- and post-natal embryo-fetal and infant development revealed no test article-related effects in infant monkeys up to six months of age.

5.6. Labeling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. With the exception of the Section 8 subheading "Pregnancy Exposure Registry", "Risk Summary" and "Data" which the applicant underlined per PLLR specifications, it is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the TRADENAME label text.

Suggested revisions to the nonclinical portions of the labeling

Recommended revisions for the nonclinical information contained in Section 8 of the labeling are made below. Refer to the clinical review for recommended revisions for the clinical information contained in Section 8 of the labeling. A clean copy of these revised labeling sections is provided in Section 13.5. Appendices.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
TRADENAME is an (b) (4) interleukin-23 (b) (4) blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on TRADENAME use in pregnant women to inform a (b) (4) drug associated risk (b) (4) of adverse developmental outcomes. Human IgG antibodies are (b) (4) known to cross the placental barrier~~,~~ ; therefore, TRADENAME may be transmitted from the mother to the developing fetus. (b) (4) In a combined embryofetal development and pre (b) (4) and post-natal development study, no adverse developmental effects were observed (b) (4) in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 30 times the maximum recommended human dose (MRHD) (b) (4) Neonatal deaths were observed (b) (4) at 6- to 30-times the MRHD ~~[(~~*see Data)*~~]~~. The clinical significance of these nonclinical findings is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

Data
Animal Data
In a combined embryofetal development and pre- and post-natal development (b) (4) study, pregnant cynomolgus monkeys (b) (4) were administered weekly subcutaneous doses of guselkumab up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal (b) (4) deaths occurred in the offspring of one (b) (4) control monkey (b) (4) (b) (4) three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD ~~(~~based on a mg/kg comparison (b) (4)) and (b) (4) three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD ~~(~~based on a mg/kg comparison (b) (4)

(b) (4) The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guselkumab is a human monoclonal IgG1λ (b) (4) antibody (b) (4) that selectively binds (b) (4) to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor (b) (4) IL-23, is a naturally occurring (b) (4) cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines. (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TRADENAME.

No effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 25 mg/kg twice weekly (15 times the MRHD based on a mg/kg comparison).

No effects on fertility parameters were (b) (4) observed (b) (4) after female (b) (4) guinea pigs (b) (4) were subcutaneously administered guselkumab at (b) (4) doses up to 100 mg/kg twice weekly (60 times the MRHD based on a mg/kg comparison) (b) (4)

Multiples of human exposure calculations based on a mg/kg comparison

Maximum recommended human dose:
100 mg ÷ 60 kg = 1.67 mg/kg

The NOAEL in monkey ePPND study = 50 mg/kg

Multiple of clinical dose:
50 mg/kg ÷ 1.67 mg/kg = 30

The NOAEL in male guinea pig fertility study = 25 mg/kg

Multiple of clinical dose:
25 mg/kg ÷ 1.67 mg/kg = 15

The NOAEL in female guinea pig fertility study = 100 mg/kg

Multiple of clinical dose:
100 mg/kg ÷ 1.67 mg/kg = 60

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

Guselkumab (also known as CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin 23 (IL-23).

- Proposed indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- Proposed dosing regimens: 100 mg administered by subcutaneous injection at Weeks 0, 4, and every 8 weeks thereafter.
- Proposed dosage forms/presentations: 100 mg/mL of guselkumab in single use prefilled syringe.

The applicant evaluated the proposed dosing regimen (100 mg administered by SC injection at Weeks 0, 4, and every 8 weeks thereafter) in three Phase 3 trials using the to-be marketed formulation/presentation. Prior to the Phase 3 trials, the applicant conducted a Phase 2 dose-ranging trial to support dose selection for Phase 3 trials, which forms the basis for dose-response and exposure-response evaluations. The applicant additionally submitted results of four Phase 1 trials in healthy subjects or subjects with psoriasis to support the pharmacokinetics (PK) and pharmacodynamics (PD) of guselkumab.

The key review findings with specific recommendations/comments are summarized below (Table 10)

Table 10: Summary of clinical pharmacology review

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	• The efficacy of guselkumab for the treatment of moderate to severe psoriasis is established in two Phase 3 trials (PSO3001 and PSO3002). • Dose-response and exposure-response analysis for efficacy based on data from Phase 2 dose ranging trials and Phase 3 trials provide supportive evidence for effectiveness.
General dosing instructions	The proposed dosing regimen (100 mg at Week 0, 4, and every 8 weeks thereafter) is acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization based on intrinsic or extrinsic factors is not recommended.
Labeling	The review team has specific content and formatting change recommendations. See Section 6.2.4 of this review
Bridge between the to-be-marketed and clinical trial formulations	• The to-be-marketed formulation was used in Phase 3 trials. • The formulation/presentation used in Phase 2 dose

	ranging trial has comparable PK as the formulation/presentation used in Phase 3 trials (see Section 13.4 for details).
Immunogenicity	• Immunogenicity may have a negative impact on systemic exposure of guselkumab. The group average trough guselkumab concentrations were similar between subjects who were positive for antibodies (ADA+) and subjects who were negative for antibodies (ADA-). However, in two pivotal Phase 3 trials, 34 of 76 ADA+ subjects had lower guselkumab trough concentrations after the formation of ADA. • The immunogenicity does not appear to impact efficacy and safety of guselkumab in most subjects in the Phase 3 trials. • The antidrug antibody (or binding antibody) assay performance is acceptable.
Pharmacodynamics	Guselkumab treatment resulted in reduced serum IL-17A, IL-17F, and IL-22 levels in subjects with psoriasis..
Disease- Drug interactions	The formation of CYP450 enzymes could be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation. Results from the clinical drug-drug interactions study (PSO1003) in subjects with moderate-to-severe psoriasis suggest that the potential for a clinically relevant drug interaction may be low for compounds metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 (except for drugs with a narrow therapeutic index). For compounds metabolized by CYP2D6, potential for a clinically relevant drug interaction cannot be ruled out.

6.1.1. Recommendations

From a clinical pharmacology standpoint, the BLA is acceptable to support the approval of TREMFYA (guselkumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

6.1.2. Post-Marketing Requirements and Commitment(s)

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanism of action (MOA) and Clinical Pharmacokinetics

MOA: Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It is believed that that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune mediated diseases, including psoriasis. By binding to the p19 subunit of IL-23, guselkumab blocks IL-23-mediated intracellular signaling, activation and cytokine production. See section 5 for additional details.

Pharmacodynamic response: Serum levels of IL-17A, IL-17F, and IL-22 were reduced after receiving 100 mg guselkumab treatment compared to pretreatment levels in subjects with moderate to severe plaque psoriasis. However, these observations were based on limited data in a subset of patients. The relationship between these pharmacodynamic changes and the mechanism(s) by which guselkumab exerts its clinical effects is unknown.

6.2.1.2. Pharmacokinetcs (PK) of guselkumab

Guselkumab exhibited linear pharmacokinetics in healthy subjects and subjects with psoriasis over the doses studied (10 mg up to 300 mg) following intravenous (IV) or subcutaneous (SC) administration. In the Phase 3 trials, serum guselkumab trough concentrations were maintained at steady-state from Week 20 onwards following SC administrations of 100 mg of guselkumab at Weeks 0 and 4, and every 8 weeks thereafter. The mean (± SD) steady-state trough serum guselkumab concentrations in the two Phase 3 trials were 1.15 ± 0.73 µg/mL and 1.23 ± 0.84 µg/mL. Serum guselkumab concentrations did not appear to accumulate over time when given SC every 8 weeks. Apparent volume of distribution (V/F) and systemic clearance (CL/F) in subjects with psoriasis were estimated to be 13.5 L and 0.516 L/day, respectively, based on population pharmacokinetic modeling analysis.

Following a single dose of 100 mg guselkumab SC study in subjects with psoriasis, mean C_{max} ranged from 4.81 to 6.24 µg/mL with T_{max} ranging from 2 – 7 days. Half-life ($T_{1/2}$) following a single 100 mg SC injection in subjects with psoriasis ranged from 14.7 to 16.9 days. Absolute bioavailability (F%) of guselkumab following a single 100 mg SC administration in healthy subjects was 48.7 %. Absolute bioavailability in subjects with psoriasis is not available because of a lack of IV PK data in subjects with psoriasis.

6.2.1.3. Drug Interactions

CYP substrates: The formation of CYP450 enzymes could be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, guselkumab could mitigate inflammation and subsequently normalize the formation of CYP450 enzymes, although a role for IL-23 in the regulation of CYP450 enzymes has not been reported.

Results from the exploratory drug-drug interactions study (PSO1003) in subjects with moderate-to-severe psoriasis suggest that the potential for a clinically relevant drug interaction may be low for compounds metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 (except for drugs

with a narrow therapeutic index). For compounds metabolized by CYP2D6 we cannot rule out the potential for a clinically relevant drug interaction. The results, however, must be interpreted with caution as there were major limitations in the study. The study only included limited number of evaluable subjects (e.g., n=7-11 for AUC) and results were variable. Further, the drug interaction assessment was done following a single dose of guselkumab which differs from the proposed therapeutic dosing regimen for subjects with psoriasis. As the proportion of study subjects who achieved IGA0/1 or PASI75 was small on Day 19 and Day 40, and presumably on Day 15 and Day 36 (the time of PK of CYP450 probe cocktails assessment), the observed drug interaction in this study may not reflect the drug interaction potential upon disease improvement after multiple doses of guselkumab.

Therefore, we recommend that in patients treated with guselkumab who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect or drug concentration should be considered and adjust individual dose of the drug as needed.

6.2.1.4. Immunogenicity

The overall incidence of antibodies to guselkumab after up to 52 weeks of exposure to guselkumab was 5.5% (N=96 out of 1730 subjects from the Phase 2 trial and all three Phase 3 trials). Of these 96 subjects who were positive for antibodies to guselkumab, 7 subjects (7.3%) were positive for neutralizing antibodies (NAbs). See section 9.5.5 for additional details.

Immunogenicity may have a negative impact on systemic exposure of guselkumab. Based on the comparison of group average trough guselkumab concentrations between subjects who were positive for antibodies (ADA+) and subjects who were negative for antibodies (ADA-) no apparent impact of antibodies on the PK of guselkumab was observed. However, comparison of the steady state trough concentration data within each ADA+ subject before and after the development of antibodies (i.e., within-subject comparison) indicated that steady state trough guselkumab levels can be reduced in ADA+ subjects. This effect wasn't consistent across all ADA+ subjects and wasn't related to the antibody titer.

With the exception of one subject, the development of antibodies to guselkumab did not appear to be associated with a reduction in the efficacy of guselkumab in most of the ADA+ subjects across the Phase 3 trials. One subject developed high ADA titer after 16 weeks of treatment and exhibited loss of efficacy.

A definitive conclusion couldn't be made about the associations between presence of antibodies to guselkumab and the development of injection site reactions (ISRs) due to the small number of ADA+ subjects who had ISRs. Further, antibody titer levels did not exhibit any consistent correlation with the development of ISRs was observed.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of 100 mg of guselkumab administered by SC injection at Weeks 0, 4, and every 8 weeks thereafter. This regimen is supported by efficacy data from two Phase 3 trials (PSO3001 and PSO3002). Refer to Section 7 of this review for efficacy findings.

Therapeutic Individualization

Therapeutic individualization is not necessary. Population PK analysis identified body weight as a significant covariate that impacted guselkumab exposure. However, efficacy data from Phase 3 trials indicated that the difference in treatment effect between guselkumab and placebo (i.e., IGA0/1 scores guselkumab minus placebo at Week 16) was consistent across all baseline weight quartiles; therefore, dose adjustment based on body weight is not recommended (see Section 6.5.2)

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of TRADENAME from a clinical pharmacology perspective.

6.2.4. Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following Labeling recommendation and comments:

Section 7 Drug Interactions:

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, guselkumab an antagonist of IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of guselkumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed. The Applicant should include a high level summary of the results from the clinical DDI study along with the limitations.

Section 12.1 Mechanism of Action: Remove potential promotional language.

Section 12.2 Pharmacodynamics: Remove (b) (4) . Further, remove (b) (4) .

Section 12.3 Pharmacokinetics: Rearrange format of content to be consistent with the current clinical pharmacology labeling guidance. Further, modify this section to include PK parameters derived from psoriasis patients instead of (b) (4) when feasible. Provide a brief description of the results from the clinical DDI study.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general pharmacology, pharmacokinetics and immunogenicity of guselkumab is provided in the table below (Table 11):

Table 11: Summary of pharmacology, pharmacokinetics and immunogenicity of guselkumab

Pharmacology	
Mechanism of Action	Guselkumab binds to the p19 protein subunit of human interleukin 23 (IL-23) with specificity and affinity. By binding to p19 subunit of IL23, 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.
Pharmacodynamics	Serum levels of IL-17A, IL-17F and IL-22 were reduced after receiving 100 mg guselkumab treatment compared to pretreatment levels in subjects with moderate to severe plaque psoriasis based on limited data in a subset of patients. However, the relationship between these pharmacodynamic changes and the mechanism(s) by which guselkumab exerts its clinical effects is unknown.
General Information	
Bioanalysis	Guselkumab concentrations in human serum were quantified using two validated bioanalytical methods; a dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) method and an electrochemiluminescence immunoassay (ECLIA) assay using the Meso Scale Discovery (MSD®) platform. Based on results from the cross validation study, the methods used for the quantification of guselkumab in human serum (i.e., ECLIA and DELFIA) are comparable. In both assays, the capture and detection reagent are specific for the variable region of guselkumab. See Section 13.4 for additional details.
PK model	A one-compartment linear model with first-order absorption and first-order elimination following SC administration adequately described the PK of guselkumab.
Heathy subjects vs subjects with psoriasis	The applicant conducted single dose studies with SC administration of guselkumab in healthy subjects (NAP1001) and subjects with psoriasis (PSO1001 Part 2 and PSO1002). Mean C_{max} and AUC_{inf} values of guselkumab following a single 100 mg SC dose were higher in healthy subjects when compared to subjects with psoriasis. However, population PK analysis didn't identify disease status as a significant covariate for the PK of guselkumab and the values for CL/F and V/F in subjects with psoriasis were comparable to the values from healthy subjects. Due to the small number of subjects in the psoriasis group (n= 5 in both PSO1001 and PSO1002) and the observed variability in PK parameters in these two studies, it is not feasible to definitively determine if there are PK differences between healthy subjects and subjects with psoriasis. See Section 13.4 for additional details.
Drug exposure at steady state	In subjects with psoriasis, steady-state serum guselkumab concentrations were achieved by Week 20 following SC administrations of 100 mg of guselkumab at Weeks 0 and 4, and every 8 weeks thereafter. The mean (± SD) steady-state trough serum guselkumab

	concentrations in the two Phase 3 trials were 1.15 ± 0.73 µg/mL and 1.23 ± 0.84 µg/mL. Serum guselkumab concentrations did not accumulate over time when given SC every 8 weeks.
Dose Linearity	Guselkumab exhibited linear pharmacokinetics in healthy subjects and subjects with psoriasis over a dose range from 10 mg to 300 mg following IV and SC injections.
Body weight	Guselkumab trough concentrations were lower in subjects with higher body weight. Population PK analysis also identified body weight as a significant covariate affecting guselkumab exposure in subjects with psoriasis. See Section 6.3.2 for additional details.
Renal or Hepatic Impairment	No formal trial was conducted to evaluate the effect of hepatic or renal impairment on the pharmacokinetics of guselkumab.
ADME	
Absorption	Following a single dose of 100 mg guselkumab SC study in subjects with psoriasis, mean C_{max} ranged from 4.81 to 6.24 µg/mL with T_{max} ranging from 2 – 7 days. Following a single dose of 100 mg in healthy subjects, guselkumab reached C_{max} of 8.01 ± 3.68 µg/mL by approximately 1 week (range of 2 to 6 days) post-dose. Bioavailability in healthy subjects following a SC dose was estimated to be 48.7 %. Absolute bioavailability in subjects with psoriasis is not available because of a lack of IV PK data in subjects with psoriasis.
Distribution	Based on population PK analysis, the estimated apparent volume of distribution (V/F) in subjects with psoriasis was approximately 13.5 L.
Elimination	Based on population PK analysis, the estimated apparent clearance (CL/F) in subject with psoriasis was 0.516 L/day. Following single dose SC administration in subjects with psoriasis, guselkumab clearance was not dose-dependent with a median half-life of 17 days. See Section 9.5 for additional details.
Metabolism	The metabolic pathway of guselkumab has not been characterized. As a human monoclonal antibody, guselkumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
Excretion	The excretion of guselkumab has not been studied. Guselkumab is a human monoclonal antibody with a molecular weight of approximately 150 kDa; therefore, intact guselkumab is unlikely to be filtered by kidney or excreted in urine.
Immunogenicity	
Incidence	The overall incidence of antibodies to guselkumab through up to Week 52 after exposure to guselkumab was 5.5% (N=96 out of 1730 subjects from the Phase 2 and three Phase 3 trials). Among subjects in the Phase 3 trials (PSO3001 and PSO3002), the incidence of antibodies to guselkumab was 6.0% (34/562).

Impact on PK	Immunogenicity may have a negative impact on systemic exposure of guselkumab. Based on the comparison of group average trough guselkumab concentration data, no apparent impact of antibodies on the PK of guselkumab was observed between subjects who were positive for antibodies and subjects who were negative for antibodies. However, comparison of the trough concentration data within each ADA+ subject before and after the development of antibodies (i.e., within-subject comparison) indicated that immunogenicity can affect the PK of guselkumab in ADA+ subjects; however, the effect wasn't consistent across ADA+ subjects and wasn't related to the antibody titer. In two Phase 3 trials, 34 of 76 ADA+ subjects had lower guselkumab trough concentrations after the formation of ADA.
Impact on efficacy	With the exception of one subject, the development of antibodies to guselkumab did not appear to be associated with a reduction in the efficacy of guselkumab in most of the ADA+ subjects across the Phase 3trials. There was, however, one subject with high ADA titer who exhibited loss of efficacy.
Impact on injection site reactions	The development of antibodies to guselkumab and titer levels did not appear to be associated with injection-site reactions.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The overall data from Phase 3 trials provide evidence that guselkumab is effective for the treatment of adult patients with moderate to severe psoriasis. The dose- and exposure-response relationships for efficacy (e.g., achieving IGA 0/1 and PASI 90 at Week 16) have provided supportive evidence of effectiveness. See Section 7 of this multi-discipline review for evaluation and details of the study design and results of the Phase 3 trials.

<u>Exposure-response for IGA (0/1) response at Week 28:</u>
The applicant conducted the exposure-response (E-R) analysis, using the steady state trough serum guselkumab concentration as the exposure variable and the percent response rate based on either IGA 0/1 or PASI 90 as the response variable. The E-R analyses were based on data at Week 28, instead of Week 16, because serum guselkumab concentration levels at Week 28 represented steady-state trough concentration for subjects randomized to guselkumab at Week 0 whereas Week 16 represented non-trough concentrations.

The analysis dataset for E-R assessment consisted of patients from the two Phase 3 trials (PSO3001 and PSO3002) who were treated with guselkumab at Week 0 and satisfy the following criterion:

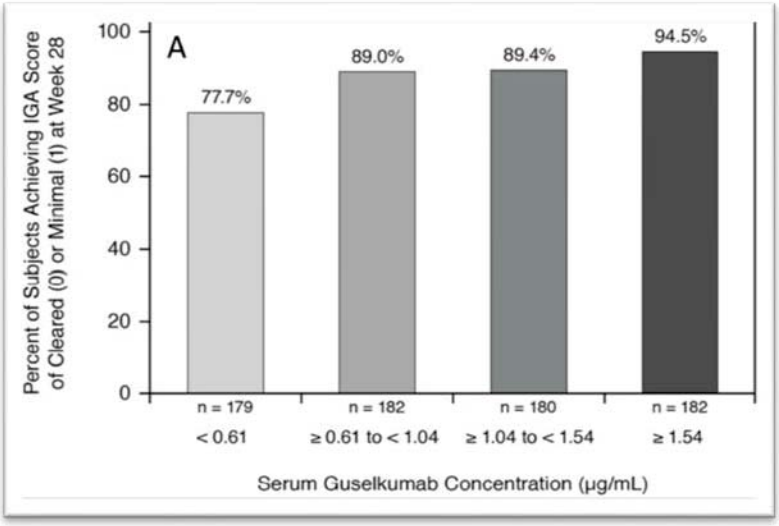
- Completed the study through at least Week 28
- Had available guselkumab concentration measurements at Week 28
- Had non-missing efficacy response variables at baseline and Week 28

A total of 723 subjects across studies PSO3001 and PSO3002 were included in the E-R analyses out of total of 823 subjects who were treated with guselkumab at Week 0.

Figure 1 shows the exposure-response relationship for the efficacy endpoint of IGA0/1 at Week 28. The IGA0/1 response rates were high, ranging from 77.7% to 94.5% across all 4 quartiles of steady-state trough serum guselkumab concentration levels in subjects from both PSO3001 and PSO3002 studies (Figure 1). Even in the lowest exposure quartile (< 0.61 µg/mL) a high IGA 0/1 response rate was observed. Similar trends were seen for PASI response rates (data not shown).

The clinical pharmacology review team has verified the E-R analysis conducted by the applicant and generally agrees with the conclusion that the E-R analysis provides supportive evidence of effectiveness. Clinical pharmacology information often provides pivotal support for evidence of effectiveness in situations that involve extrapolation of findings (e.g., effectiveness) of an approved product to a new population (e.g., adult to pediatric), or a different dose, dosing regimen, or dosage form.

Figure 1: Percent of guselkumab treated subjects (Trials PSO3001 and PSO3002) achieving IGA score of cleared (0) or minimal (1) at Week 28 by trough serum guselkumab concentrations at Week 28 presented in 4 quartiles



Source: Figure 14 from applicant's summary of clinical pharmacology

6.3.2.2. Does the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen, 100 mg administered by SC injection at Weeks 0, 4, and every 8 weeks thereafter, is appropriate. The supporting evidence includes primary efficacy and safety results in the Phase 3 trials which evaluated the proposed dose regimen and demonstrated efficacy across Week 16 to Week 48. Results from the Phase 2 dose ranging trail supported the dose selected for the Phase 3 trials.

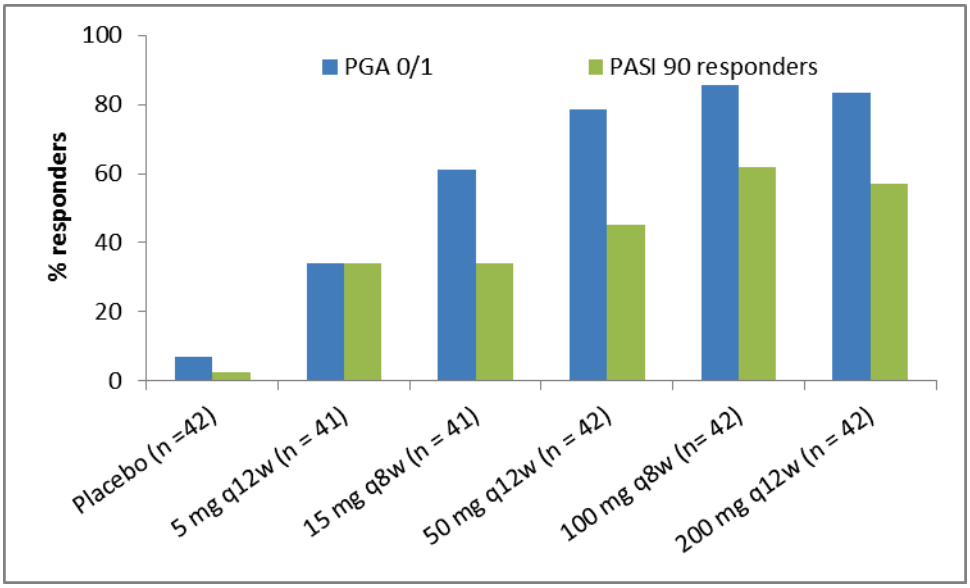
Primary efficacy data from Phase 3 trials:

The primary efficacy results from the guselkumab Phase 3 trials are described in Section 7 of this multi-discipline review.

Phase 2 dose ranging trial supported the Phase 3 trial dose regimen:
The Phase 3 trials only evaluated one dose regimen which was selected based on outcomes from the Phase 2 dose-ranging trial (PSO2001). The Phase 2 trial evaluated five different dosing regimens including 5 mg q12w, 15 mg q8w, 50 mg q12w, 100 mg q8w, and 200 mg q12w. The study evaluated effect of guselkumab at multiple time points based on PGA score and PASI scores.

Figure 2 illustrates the dose-response relationship using PASI 90 and PGA 0/1 at Week 16 in the Phase 2 dose ranging study. A clear dose-response relationship was observed across both response measures (PASI90 and PGA0/1) at Week 16 (Figure 2).

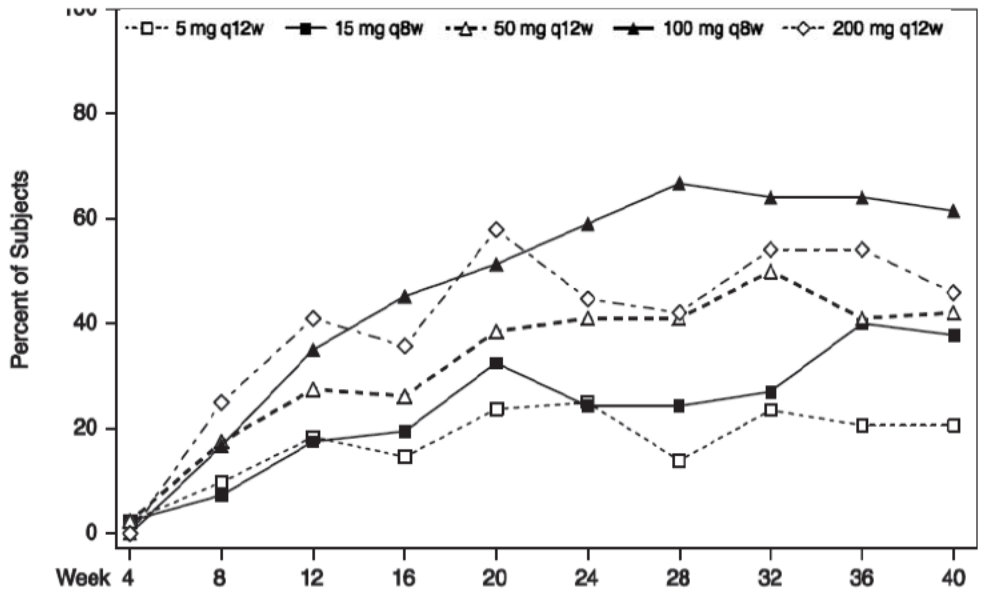
Figure 2: Dose-response for efficacy endpoints from guselkumab Phase 2 study at Week 16.



Data source: Reviewer generated plot based on data from CSR CNTO1959PSO2001

Figure 3 illustrates the time course of response rate based on the proportion of subjects achieving a PGA score of cleared (0) or minimal (1) for all groups treated with guselkumab. In comparing the 100 mg q8w versus 200 mg q12w dose regimen, lower response rates are observed for the 200 mg q12w dosing group after Week 20 (Figure 3.3.2.b). Furthermore, the time course of response rate for 200 mg q12w dose regimen showed a decline within the dosing interval, e.g., after the dose at Week 16 the response rate peaked at Week 20 and reduced at Week 24 and Week 28. These observations support the selection of q8w dosing interval for the Phase 3 studies.

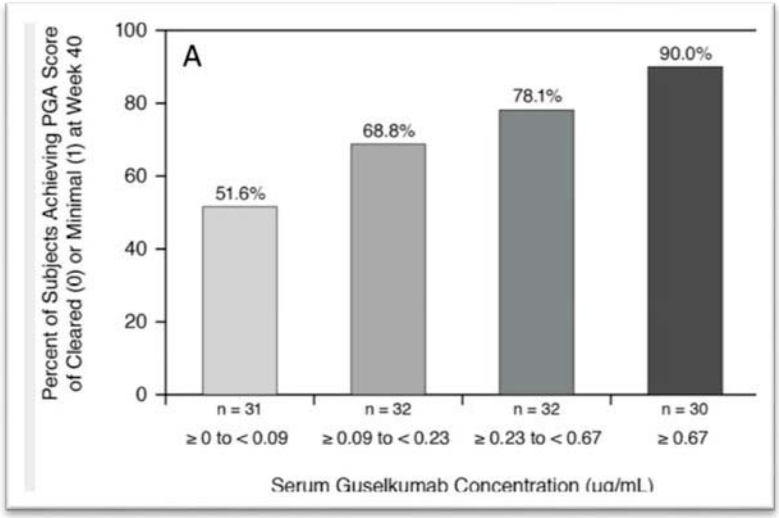
Figure 3 : Time course of percentage of subjects with PGA Scores of Cleared (0) or Minimal (1) from Week 4 (first efficacy assessment post dose) through Week 40 in guselkumab Phase 2 study.



Source: Adapted from Figure 6 of applicant's summary of clinical efficacy)

Exposure-response analysis indicated that higher steady-state trough serum guselkumab concentrations were associated with higher clinical efficacy over the dose range studied (Figure 4) To assess the relationship between serum guselkumab concentrations and efficacy, the steady-state trough serum guselkumab concentrations at Week 40 were divided into four distribution quartiles. Subjects with trough serum guselkumab concentrations ≥0.67 µg/mL achieved the highest levels of efficacy at Week 40 based on PASI and PGA scores. A total of 125 subjects across studies PSO2001 had available data and were included in the E-R analyses out of 208 subjects who were treated with guselkumab at Week 0.

Figure 4 : Percent of guselkumab treated subjects achieving PGA Score of Cleared (0) or Minimal (1) at Week 40 by trough serum guselkumab concentrations at Week 40 presented in 4 quartiles based on data from the Phase 2 dose ranging study



Source: Figure 11 from Applicant's summary of clinical pharmacology

Exposure-response for safety:

Overall, guselkumab (100 mg at Weeks 0, 4 and q8w thereafter) was well-tolerated.

Table 12 summarizes the incidence of treatment-emergent adverse events (TEAE) through Week 28 in subjects treated with guselkumab categorized by steady state trough serum guselkumab concentrations at Week 28 presented in 4 quartiles: <0.61 µg/mL (1st quartile), ≥0.61 to <1.04 µg/mL (2nd quartile), ≥1.04 to <1.54µg/mL (3rd quartile), and ≥1.54µg/mL (4th quartile).

Table 12: Incidence of treatment-emergent adverse events through Week 28 in subjects treated with guselkumab 100 mg at Week 0 distributed by steady state trough serum guselkumab concentrations at Week 28 presented in 4 quartiles (Studies PSO3001 and PSO3002)

	Guselkumab Concentration Quartile			
	< 1st Quartile	≥ 1st Quartile to < 2nd Quartile	≥ 2nd Quartile to < 3rd Quartile	≥ 3rd Quartile
Analysis set: Subjects treated	179	182	180	182
Avg duration of follow-up (weeks)	28.52	28.35	28.25	28.19
Avg exposure (number of administrations)	17.76	17.75	17.69	17.68
Subjects with 1 or more adverse events	102 (57.0%)	116 (63.7%)	104 (57.8%)	121 (66.5%)
Subjects with 1 or more serious adverse events	8 (4.5%)	6 (3.3%)	3 (1.7%)	3 (1.6%)
Subjects with 1 or more infections	57 (31.8%)	59 (32.4%)	55 (30.6%)	80 (44.0%)
Subjects with 1 or more infections requiring treatment	19 (10.6%)	20 (11.0%)	16 (8.9%)	24 (13.2%)
Subjects who discontinued study agent because of adverse events	1 (0.6%)	1 (0.5%)	0	1 (0.5%)

Note: 1st quartile = 0.61 µg/mL, 2nd quartile = 1.04 µg/mL, 3rd quartile = 1.54 µg/mL are based on subjects in the guselkumab 100 mg group.

Source: Table 18 from of applicant's summary of clinical pharmacology

In subjects with serum guselkumab concentrations in the highest quartile (≥1.54µg/mL), higher rates of infections were observed compared with subjects in the three lower quartiles (44 % versus approx. 32 %). However, the rate of infection was similar among three lower exposure quartiles. Beyond infections, the occurrence of SAE appeared to have no consistent trend across the guselkumab exposure quartiles.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. A dose adjustment based on body weight is not necessary based on the available efficacy data in Phase 3 trials.

The applicant evaluated various intrinsic factors, including baseline body weight, race, age, sex, baseline albumin and CRP, baseline PASI in the population PK analysis. The analysis identified baseline body weight as a significant covariate that can influence guselkumab PK. **Table 13** illustrates the effect of body weight effect on CL/F and V/F. The median body weight was 87.1 kg in the population PK database which includes subjects from Trial PSO2001, PSO3001, and PSO3002. As illustrated in Table 3.3.3.a. a subject weighing 100 kg (75th percentile of body weight) has greater CL/F and V/F values, by 33% and 27%, respectively, compared to a subject weighing 74.8 kg (25th quartile of body weight). See Section 13.4 for additional details of the population PK analysis and covariate analysis results.

Table 13: Summary of body weight effect on CL/F and V/F of subjects with psoriasis based on population PK modeling

	Allometry Exponent*	Comparing Parameter value for a 100-kg subject to the reference subject with BW of 74.8 kg	
		Geometric Ratio	90 % Confidence Interval
BW effect on CL/F	0.998	1.33	(1.31, 1.36)
BW effect on V/F	0.829	1.27	(1.25. 1.30)

* The covariate of body weight in the population model is implemented as an exponential function
$CL/F = CL/F_{reference\ subject} \times (BW/87.1)^{exponent} \times 1.12^{diab} \times 1.11^{race}$
$V/F = V/F_{reference\ subject} \times (BW/87.1)^{exponent}$
Data source: Table 8 from population PK analysis

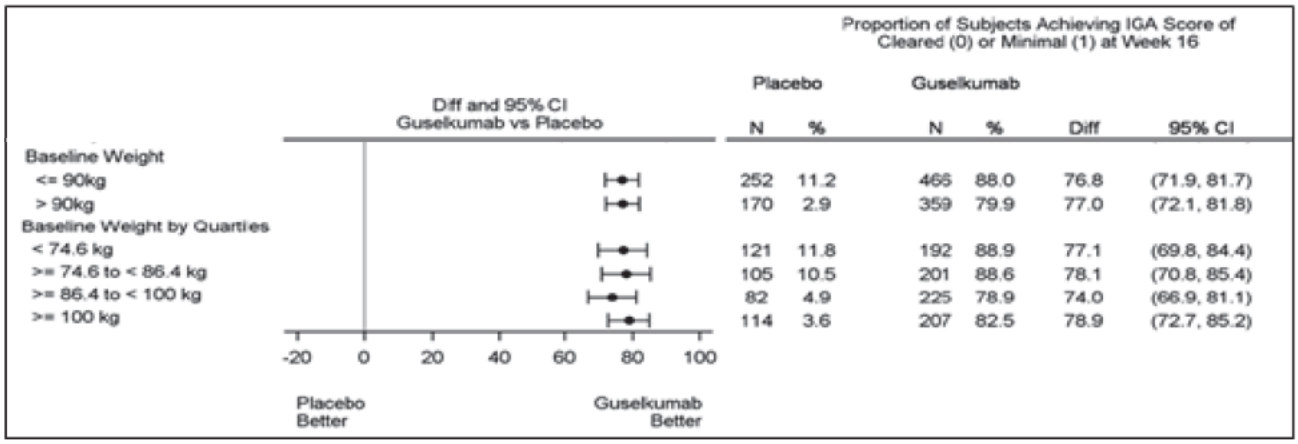
Table 14: Summary of trough serum guselkumab concentrations in study PSO3001 and PSO3002 at Week 28 in guselkumab treated subjects stratified by body weight

	Body weight > 90 kg*	Body weight ≤ 90 kg
N	315	415
Median (min, max)	0.827 (0.0262, 4.99)	1.20 (0.0171, 4.51)
Mean (SD)	0.937 (0.645)	1.35 (0.818)

* The median body weight of subjects in study PSO3001 and PSO3002 is 90 kg.
Source: Reviewer generated table based on data from Modeling and Simulation Analysis Report

However, alternative dosing regimens adjusting for body weight is not necessary based on the efficacy data in Phase 3 trial. The median weight (87.1 kg) of subjects in the guselkumab Phase 3 trials approximated 90 kg. At Week 28 the median trough serum guselkumab concentrations was lower among subjects weighing >90 kg compared to subjects weighing ≤ 90 kg (Table 14). Subgroup analysis of the pooled data from Trials PSO3001 and PSO3002 at Week 16 indicated that the difference in treatment effect between guselkumab and placebo (i.e., IGA0/1 scores guselkumab minus placebo) was consistent across all baseline weight quartiles (Figure 5); therefore, dose adjustment based on body weight is not necessary.

Figure 5: Effect of baseline body weight on proportion of subjects achieving IGA 0/1 at Week 16 in Phase 3 studies PSO3001 and PSO3002



Source: Adapted from appendix 2 from summary of clinical efficacy

6.3.2.4. Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

Results from the exploratory drug-drug interactions study (PSO1003) in subjects with moderate-to-severe psoriasis suggest that the potential for a clinically relevant drug interaction may be low for compounds metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 (except for drugs with a narrow therapeutic index). For compounds metabolized by CYP2D6 we cannot rule out the potential for a clinically relevant drug interaction. Overall, we recommend that in patients treated with guselkumab who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect or drug concentration should be considered and the individual dose of the drug adjusted as needed.

The Applicant conducted the drug-drug interaction study (PSO1003) in adult subjects with moderate-to-severe psoriasis which was an exploratory study. The major limitations of this study include the limited number of evaluable subjects (e.g., n=7-11 for AUC) and the observed high variability. Further, the drug interaction assessment was done following a single dose of guselkumab which differs from the proposed therapeutic dosing regimen for subjects with psoriasis. As the proportion of study subjects who achieved IGA0/1 or PASI75 was small on Day 19 and Day 40, and presumably on Day 15 and Day 36 (the time of PK of CYP450 probe

cocktails assessment), the observed drug interaction in this study may not reflect the drug interaction potential upon disease improvement after multiple dose of guselkumab.

Study PSO1003 evaluated 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]). The probe cocktail was administered on Days 1, 15, and 36; a single SC dose of 200 mg guselkumab administered on Day 8. A total of 17 subjects with psoriasis were enrolled into the study, 14 subjects received treatment with guselkumab, and 12 subjects completed the study, i.e., received all planned dose administrations of probe cocktails and guselkumab.

Table 15 summarizes the PK parameters (C_{max} and AUC_{inf}) along with the geometric mean ratios (GMRs) of all the probe substrates before (Day 1) and after (Day 15 and Day 36) guselkumab administration. The wide 90 % confidence intervals of the GMRs (Day 15/Day 1 and Day 36/Day 1) for C_{max} and AUC_{inf} (shown in Table 1) indicate that the changes in C_{max} and AUC_{inf} after guselkumab administration were variable.

For all the probe substrates, the mean GMR for AUC_{inf} was less than 1.25. The upper bounds of the 90 % CI for the GMR (Day 15/Day 1 and Day 36/Day 1) for AUC_{inf} was less than 2.0 for midazolam, S-warfarin, omeprazole and caffeine suggesting that the potential for a clinically relevant drug interaction may be low for compounds metabolized via CYP3A4, CYP2C9, CYP2C19 and CYP1A2 (except for narrow therapeutic index drugs).

However, the upper bound of the 90 % CI for the GMR for dextromethorphan were greater than 2 and greater than 3, respectively for Day 15/Day 1 and Day 36/Day 1. Analysis of the individual data (See appendix for details) for dextromethorphan revealed that only one individual out of 10 subjects exhibited greater than 2-fold change in AUC_{inf} after guselkumab treatment (Day 36). As a result, we cannot rule out the potential for a clinically relevant drug interaction for compounds metabolized via CYP2D6.

Table 15: Summary of C_{max} and AUC_{inf} for all probe substrates on Day 1 (prior to guselkumab administration), Day 15 and Day 36 in subjects with moderate-to-severe psoriasis.

	C_{max} (ng/mL)							
	Day 1		Day 15			Day 36		
	N	Mean (SD)	N	Mean (SD)	GMR (90 % CI)	N	Mean (SD)	GMR (90 % CI)
Midazolam	13	13.22 (6.983)	11	14.62 (6.794)	1.112 (0.752 - 1.645)	11	15.15 (7.964)	1.137 (0.765 - 1.690)
S-Warfarin	16	582.94 (159.702)	13	618.69 (132.677)	1.067 (0.900 - 1.265)	12	540.00 (142.465)	0.904 (0.736 - 1.110)
Omeprazole	15	350.60 (132.607)	12	331.25 (130.839)	0.958 (0.717 - 1.281)	11	330.91 (175.493)	0.955 (0.671 - 1.359)
Dextromethorphan	15	1.78 (2.041)	12	2.12 (2.722)	1.055 (0.457 - 2.434)	11	2.52 (3.266)	1.326 (0.553 - 3.181)
Caffeine	16	2096.25 (533.540)	13	2166.15 (358.900)	1.073 (0.940 - 1.224)	11	2183.64 (499.945)	1.058 (0.888 - 1.262)
	AUC_{inf} (ng.h/mL)							
	Day 1		Day 15			Day 36		
	N	Mean (SD)	N	Mean (SD)	GMR (90 % CI)	N	Mean (SD)	GMR (90 % CI)
Midazolam	13	49.80 (24.007)	11	51.16 (22.885)	1.005 (0.697 - 1.449)	11	51.47 (23.100)	1.039 (0.749 - 1.442)
S-Warfarin	14	18398.20 (6037.814)	13	20774.21 (5871.501)	1.124 (0.903 - 1.398)	11	19522.47 (5725.991)	1.054 (0.817 - 1.361)
Omeprazole	13	1029.90 (686.644)	11	952.75 (646.786)	0.964 (0.613 - 1.517)	7	795.60 (369.740)	1.193 (0.749 - 1.900)
Dextromethorphan	12	23.00 (29.627)	9	17.23 (21.690)	1.127 (0.558 - 2.275)	10	26.43 (33.847)	1.240 (0.464 - 3.314)
Caffeine	16	22766.71 (12311.993)	12	21019.15 (8215.748)	1.004 (0.770 - 1.311)	11	20856.91 (7874.459)	1.018 (0.765 - 1.354)

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The development program for guselkumab for the treatment of moderate to severe plaque psoriasis in adults included 6 clinical trials (Core Trials). The applicant submitted supportive safety data from 5 additional trials conducted in other populations (Japanese) or other indications [palmoplantar pustulosis (PPP), rheumatoid arthritis (RA) and generalized pustular psoriasis (GPP) or erythrodermic psoriasis (EP)].

Core Trials

Phase 3 Trials: cutoff date (6/30/2016)

- CNTO1959PSO3001 (VOYAGE 1, PSO3001, Trial 3001): safety and efficacy
- CNTO1959PSO3002 (VOYAGE 2, PSO3002, Trial 3002): safety and efficacy
- CNTO1959PSO3003 (NAVIGATE, PSO3003, Trial 3003): data to support comparative claim

Phase 2 Trial:

- CNTO1959PSO2001 (X-PLORE, PSO2001) randomized, placebo- and active-comparator controlled, parallel-group, dose-ranging, 7-arm trial in subjects with moderate to severe plaque psoriasis.

Phase 1 Trials:

- CNTO1959PSO1001 (PSO1001) single dose, first-in-human trial in healthy subjects (Part 1) and subjects with moderate to severe plaque psoriasis (Part 2)
- CNTO1959PSO1002 (PSO1002) randomized, double-blind, placebo-controlled, ascending single-dose trial in Japanese subjects with moderate to severe plaque psoriasis

Supportive Trials

- CNTO1959NAP1001 (NAP1001): Phase 1 PK comparability trial in healthy volunteers (HV)
- CNTO1959NAP1002 (NAP1002): Phase 1 assessment of glycoform variants trial in HV
- CNTO1959PPP2001 (PPP2001): Phase 2 trial in Japanese subjects with PPP
- CNTO1275ARA2001 (ARA2001): Phase 2 trial in subjects with RA
- CNTO1959PSO3005 (PSO3005): ongoing trial in Japanese subjects with GPP and EP

Table 16 provides a summary of all trials pertinent to the evaluation of the efficacy and safety of guselkumab for the treatment of moderate to severe plaque psoriasis. For a discussion of the pharmacokinetic trials (including drug-drug interaction studies) the reader is refer to Section 6 of this review).

Table 16: Core Clinical Trials: BLA 761061

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subject	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
3001 VOYAGE 1	Phase 3, multicenter, randomized, double blind placebo and active-comparator-controlled trial to assess safety and efficacy	Placebo SC (n=174) Weeks 0, 4, and 12 with cross over at Week 16 to guse kumab 100 mg SC at Weeks 16 and 20 followed by q8w through Week 44 Guse kumab 100 mg SC (n=329) Weeks 0, 4, and 12, followed by q8w through Week 44 Adalimumab SC (n=333) 80 mg at Week 0 and 40 mg at Weeks 1, 3, and 5, followed by 40 mg q2w through Week 47 Open-label extension: All subjects receive guse kumab 100 mg SC at Week 52 and q8w to Week 160	Primary proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieved a PASI 90 response at Week 16 (Guselkumab compared to placebo)	Database lock at Week 48	Enrolled 837 Treated 836 Gus 329 Plac 174 Ada 333 US Ada 115 PP 788	Males and females age ≥ 18 years with moderate to severe plaque-type psoriasis with or without PsA for at least 6 months who were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12, PGA score ≥3 and BSA ≥10%.	101 sites in 10 countries Canada=11 US=27 Hungary=6; Poland=7 Russia=12; Germany= 14 Spain=5; Australia=7 Korea =6 Taiwan=6.
3002 VOYAGE 2	Phase 3, multicenter, randomized, double-blind placebo- and active-comparator-controlled trial with randomized withdrawal and retreatment to assess safety and efficacy	Placebo SC (n=248) Weeks 0, 4, and 12 followed by guselkumab 100 mg at Weeks 16 and 20. At Week 28: -PASI 90 nonresponders continued guselkumab 100 mg SC q8w. -PASI 90 responders received placebo until loss of ≥50% of PASI improvement at Week then re-treated with guse kumab 100 mg SC q8w.	Primary proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieved a PASI 90 response at Week 16 (Guselkumab compared to placebo)	Database lock at Week 48	Enrolled 993 Treated 992 Gus 496 Plac 248 Ada	Males and females age ≥ 18 years with moderate to severe plaque-type psoriasis with or without PsA for at least 6 months who were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12,	115 sites in 9 countries Canada=10 Czech=7 US=31 Poland=18 Russia=11 Germany= 10 Spain=9 Australia=6 Korea =13

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subject	Study Population	No. of Centers and Countries
		Guse kumab 100 mg SC (n=494) Weeks 0, 4, 12, and 20. At Week 28: -PASI 90 nonresponders continued guselkumab 100 mg SC q8w. -PASI 90 responders were re-randomized to guselkumab 100 mg SC q8w or placebo. Upon loss of ≥50% of PASI improvement at Week 28, subjects receiving placebo were re-treated with guse kumab 100 mg SC, followed by dosing 4 weeks later, and then q8w. Adalimumab SC (n=248) 80 mg SC at Week 0 followed by 40 mg at Week 1 and q2w thereafter through Week 23. At Week 28: -PASI 90 non-responders initiated guse kumab 100 mg SC, followed by dosing 4 weeks later, and then q8w. -PASI 90 responders received placebo. Upon loss of ≥50% of PASI improvement at Week 28, subjects initiated guse kumab 100 mg SC, followed by dosing 4 weeks later, and then q8w. Open-label extension: All subjects receive			248 US Ada 81	PGA score ≥3 and BSA ≥10%.	

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subject	Study Population	No. of Centers and Countries
		guse kumab 100 mg SC q8w starting at Week 76.					
3003 VOYAGE 3	Phase 3, multicenter, randomized, double-blind active- controlled trial with an open label run-period to assess comparative safety and efficacy	Open-label Weeks 0 and 4 (n=871) (Subjects weighing ≤100 kg received ustekinumab 45 mg and >100 kg received ustekinumab 90 mg) At Week 16, subjects with IGA≥2 randomized 1:1 to: -Guselkumab 100 mg (n=135) Weeks 16 and 20, then q8w -Ustekinumab (n=133) Weeks 16, 28, and 40 Subjects with an IGA=0 or 1 continued ustekinumab at Weeks 16, 28, and 40 (n=585)	Primary #of visits at which subjects achieve an IGA response of 0 or 1 and at least a 2-grade improvement (from Week 16) from Week 28 through Week 40 among randomized subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16.	Database lock at Week 40	Enrolled 871 At Week 16: 585 had IGA=0/1 268 had IGA ≥2 135:Gus 133:Ust	Males and females age ≥ 18 years with moderate to severe plaque-type psoriasis with or without PsA for at least 6 months who were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12, PGA score ≥3 and BSA ≥10%. All randomized subjects received ustekinumab.	100 sites in 10 countries Canada=8 US=31 UK=4 Poland=19 Russia=8 Germany=10 Spain=5 Australia=4 Korea =7 Taiwan=5
Studies to Support Safety							
PSO2001 X-PLORE	Phase 3, multicenter, randomized, placebo- and active-comparator-controlled, dose-ranging trial to assess safety and efficacy	Placebo SC (n=42) Weeks 0, 4, and 8 followed by guse kumab 100 mg q8w beginning at Week 16 Guse kumab 5 mg SC (n=41) Weeks 0, 4, and 16 followed by q12w regimen Guse kumab 15 mg SC (n=41) Weeks 0, 8, and 16 followed by q8w regimen Guse kumab 50 mg SC (n=42) Weeks 0, 4, and 16 followed by q12w regimen Guse kumab 100 mg SC	Primary proportion of subjects who achieved a score of cleared (0) or minimal (1) on the PGA at Week 16 Major secondary 1.proportion of subjects who achieved a PASI 75 response at Week 16. 2. difference of the	Screening phase: 4 weeks Treatment phase: 40 weeks Follow-up 12 weeks	293 Plac: 42 Gus:207 Ada: 43 US Ada: 21	Males and females age ≥ 18 years with moderate to severe plaque-type psoriasis with or without PsA for at least 6 months. Moderate to severe psoriasis defined as PASI score ≥12, PGA score ≥3 and BSA ≥10%.	31 sites in N. America 12 sites in Europe

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subject	Study Population	No. of Centers and Countries
		(n=42) Weeks 0, 8, and 16 followed by q8w regimen Guse kumab 200 mg SC (n=41) Weeks 0, 4, and 16 followed by q12w regimen Adalimumab SC (n=43) 80 mg SC at Week 0, 40 mg SC at Week 1, and 40 mg q2w	PGA score of (0) or (1) response rate between guselkumab groups and adalimumab treatment group at Weeks 16 and 40 3. Change in DLQI from baseline at Week 16				
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
PSO1002	Phase 1, randomized, double-blind, placebo controlled, and ascending single-dose trial to assess safety and tolerability	Part 1: 0.03, 0.1, 0.3, 1, 3, 10 mg/kg IV or 3 mg/kg SC dose of guselkumab (lyophilized) or placebo Part 2: 10, 30, 100, 300 mg SC dose of guselkumab (lyophilized) or placebo	-Safety outcomes -PK parameters: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL, $C_{L/F}$, Vz, V_z/F, V_{ss}, MRT, and F% -Antibodies to gus -PASI, PGA	Single dose Follow-up Part 1: 16 Weeks Part 2: 24 Weeks	Part 1: 47 Part 2: 24	Part 1: Healthy and 18 to 55 years old, Part 2: Subjects aged 18 to 65 years with plaque psoriasis for ≥ 6 months prior to dosing	6 sites in the US
PSO1002	Phase: 1 randomized, double-blind, placebo-controlled, ascending single-dose trial to assess safety and tolerability	10, 30, 100, or 300 mg single SC dose of guse kumab or placebo (n=4: placebo; n=5 each: 10, 30, 100 and 300 mg guse kumab)	-Safety outcomes -PK parameters: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, Vd_2/F -Antibodies to gus -PASI, PGA	Single dose Follow-up 24 Weeks	24 5 gus:1 plac in each of 4 cohorts	Subjects aged 20 to 65 years inclusive, with moderate to severe plaque psoriasis	1 site in Japan

Source: Reviewer's table
Guselkumab=Gus; Placebo=Plac; Adalimumab=Ada; Ustekinumab=Ust
PP=Per-Protocol population
ITT=Intent-To-Treat population

7.1.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of guselkumab for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format are located in the following network path:

- Original submission: \\cdsesub5\EVSPROD\BLA761061\0000\m5\datasets

Data and Analysis Quality

In collaboration with the Office of Computational Science (OCS), the statistical and clinical team evaluated the data fitness. This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the following:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata.

In general, the data submitted by the applicant to support the efficacy and safety of guselkumab for the proposed indication appeared acceptable. Observations regarding the data quality included:

- Actual Treatment (EXTRT) has the value 'Not Available' (3002, 3003); Exposure Start Date (EXSTDTC) and Exposure End Date (EXENDTC) are both missing (<1% of subjects in the Phase 3 trials); Screen failures do not have records in the Inclusion/Exclusion (IE) domain (6-19%);
- In all trials, treatment emergent flags for AEs are not included in the SDTM, only in the analysis dataset (ADaM).
- Treatment arm variables (ARM and ACTARM) contain confusing values and capture multiple treatments across trial phases. Subjects in all trials were allowed to rescreen and may have more than one subject identifier (Previous subject identifier: PSUBJID)
- Some subjects in the safety population of all trials were randomized or enrolled but did not receive any treatment.
- In the Demographics (DM) domain, race values included 'Other', 'Multiple', 'Unknown', or 'Not Reported' which complicated the analysis

A final statistical analysis plan (SAP) was submitted and most relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Pivotal Phase 3 Trials (Trials 3001 & 3002)

7.2.1.1. Study Design and Endpoints

The applicant conducted two pivotal Phase 3 trials (Trials 3001 and 3002). For both trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years of age or older
- Diagnosis of plaque psoriasis for at least 6 months
- Candidates for either systemic therapy or phototherapy
- Have moderate-to-severe plaque psoriasis at screening and baseline defined by:
  - Investigator Global Assessment (IGA) score of at least 3 (moderate), see Figure 21 in Appendix 13.3 for details on the IGA scale
  - Psoriasis Area and Severity Index (PASI) ≥12, see Figure 22 in Appendix 13.3 for details on the calculation of PASI
  - Body Surface Area (BSA) ≥10%

Subjects with non-plaque forms of psoriasis (e.g., erythrodermic, guttate, or pustular) or with drug-induced psoriasis (e.g., a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) were excluded. Subjects who had ever received guselkumab or adalimumab were also excluded.

Figure 6 and Figure 7 present the study designs for Trials 3001 and 3002, respectively. Both were multicenter, randomized, double-blind, placebo and active-controlled (adalimumab), parallel-group, Phase 3 trials evaluating the safety and efficacy of guselkumab for the treatment of moderate-to-severe plaque psoriasis. The first 24 weeks of Trials 3001 and 3002 were identical in terms of treatment and assessments. In addition, the randomization was stratified by investigational site in both trials.

Trial 3001 consisted of the following two periods: a blinded treatment period (Week 0 through Week 48) and an open-label treatment period (after Week 48 through Week 160).

- **Blinded Treatment Period**: the protocol specified randomizing approximately 750 subjects to one of the following treatment arms in a 2:1:2 ratio:
  - **Group I (N=300):** guselkumab 100 mg at Weeks 0, 4, 12, and every 8 weeks (Q8W) thereafter through Week 44, placebo for guselkumab at Week 16, and placebo for adalimumab at Weeks 0, 1, 3, 5, and every 2 weeks (Q2W) thereafter through Week 47 to maintain the blind.
  - **Group II (N=150):** placebo for guselkumab at Weeks 0, 4, and 12, and placebo for adalimumab at Weeks 0, 1, 3, 5, and Q2W through Week 15 to maintain the blind. At Week 16, these subjects switched to receive guselkumab 100 mg at Weeks 16, 20, and Q8W thereafter through Week 44, and placebo for adalimumab at Week 17 and Q2W thereafter to maintain the blind.
  - **Group III (N=300):** adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Weeks 1, 3, 5, and Q2W thereafter through Week 47 and placebo for guselkumab at Weeks 0, 4, 12, 16, and 20, and Q8W thereafter through Week 44 to maintain the blind.

- **Open-Label Treatment Period**: subjects in Groups I and II continued to receive guselkumab 100 mg Q8W from Week 52 through Week 148, and subjects in Group III

(originally randomized to adalimumab) entered a washout period after their final dose of adalimumab at Week 47 and initiated guselkumab 100 mg at Week 52 and then Q8W thereafter through Week 148.

- Subjects were evaluated at screening, baseline (Week 0), and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, and 160.

Trial 3002 consisted of the following three periods: active comparator-controlled period (Week 0 through Week 24), a randomized withdrawal and retreatment period (Week 28 up to Week 76), and an open-label treatment period (Week 76 through Week 160).

- **Active Comparator -Controlled Period**: the protocol specified randomizing approximately 1000 subjects to one of the following treatment arms in a 2:1:1 ratio:
  - **Group I (N=500):** guselkumab 100 mg at Weeks 0, 4, 12, and 20, placebo for guselkumab at Week 16 and placebo for adalimumab at Weeks 0, 1, 3, 5, and Q2W through Week 23 to maintain the blind.
  - **Group II (N=250):** placebo for guselkumab at Weeks 0, 4, and 12, and placebo for adalimumab at Weeks 0, 1, 3, 5, and Q2W through Week 15 to maintain the blind. At Week 16, these subjects switched to receive guselkumab 100 mg at Weeks 16 and 20, and placebo for adalimumab at Weeks 17, 19, 21, and 23.
  - **Group III (N=250):** adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Weeks 1, 3, 5, and Q2W through Week 23 and placebo for guselkumab at Weeks 0, 4, 12, 16, and 20.

- **Randomized Withdrawal and Retreatment Period**: beginning at Week 28, treatment for all subjects was based on their level of response (i.e., ≥ 90% improvement in PASI (PASI 90) from baseline) at that visit.
  - ***Subjects Originally Randomized to Guselkumab (Group I):***
    - **Group Ia**: PASI 90 non-responders at Week 28 received guselkumab 100 mg at Weeks 28, 36, and Q8W thereafter, and placebo for guselkumab at Weeks 32, 40, and Q8W thereafter to maintain the blind.
    - PASI 90 responders at Week 28 were re-randomized in a 1:1 ratio to:
      - **Group Ib:** guselkumab 100 mg at Weeks 28, 36, and Q8W thereafter, and placebo for guselkumab at Weeks 32, 40, and Q8W thereafter to maintain the blind.
      - **Group Ic:** placebo for guselkumab at Week 28 and Q4W thereafter until they either lose ≥50% of their Week 28 PASI response prior to Week 72 or they reach Week 72 before they lose ≥50% of their Week 28 PASI response. When one of these events occurs, subjects will reinitiate guselkumab 100 mg treatment at that visit, 4 weeks later, and then Q8W thereafter. These subjects also received placebo administrations as needed to maintain the blind up to Week 72.
  - ***Subjects Originally Randomized to Placebo (Group II):***
    - **Group IIa**: PASI 90 non-responders received guselkumab 100 mg at Weeks 28, 36, and Q8W thereafter, and placebo for guselkumab at Weeks 32, 40, and Q8W thereafter until Week 72.
    - **Group IIb:** PASI 90 responders received placebo for guselkumab at Week 28 and Q4W thereafter until they either lose ≥50% of their Week 28 PASI response prior to Week 72 or they reach Week 72 without losing ≥50% of their Week 28 PASI response. When one of these events occurs, subjects reinitiated guselkumab 100

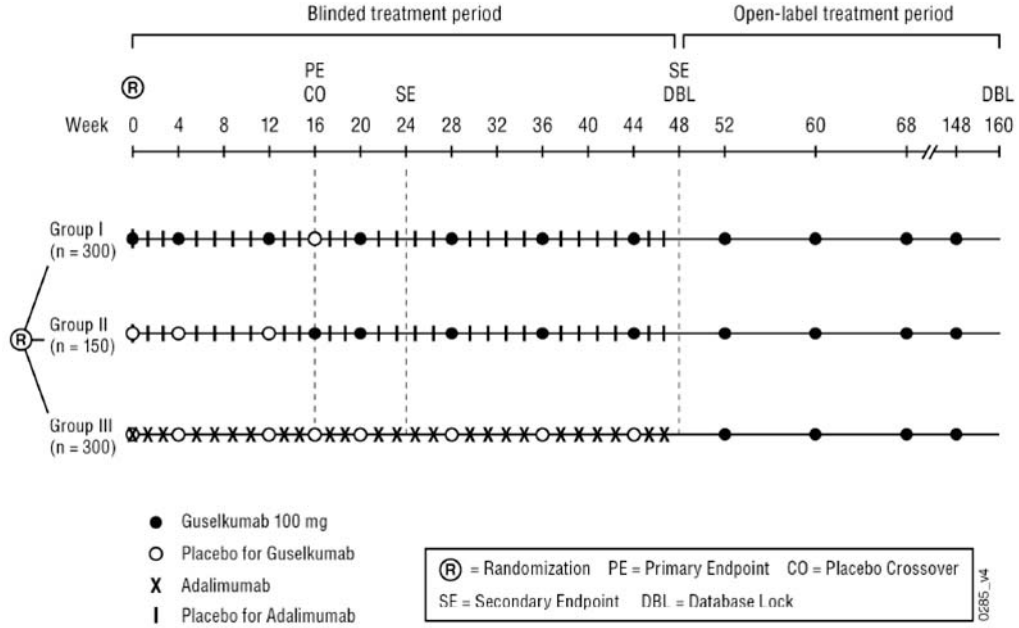
mg treatment at that visit, 4 weeks later, and then Q8W thereafter. These subjects also received placebo administrations as needed to maintain the blind up to Week 72.

- ***Subjects Originally Randomized to Adalimumab (Group III):***
  - **Group IIIa:** PASI 90 non-responders received guselkumab 100 mg at Weeks 28, 32, and Q8W thereafter, and placebo for guselkumab at Weeks 36, 44, and Q8W thereafter until Week 68.
  - **Group IIIb:** PASI 90 responders received placebo for guselkumab at Week 28 and Q4W thereafter until they either lose ≥50% of their Week 28 PASI response prior to Week 72 or they reach Week 72 without losing ≥50% of their Week 28 PASI response. When one of these events occurs, subjects initiated guselkumab 100 mg treatment at that visit, 4 weeks later, and then Q8W thereafter. They also received placebo administrations as needed to maintain the blind up to Week 72.

- **Open-Label Treatment Period (from Week 76 through Week 160)**: all subjects received guselkumab100 mg Q8W starting at Week 76. Subjects had study visits Q8W through Week 148 with a subsequent safety follow-up visit at Week 160. Study drug was self-administered by the subject at the study site during this period.

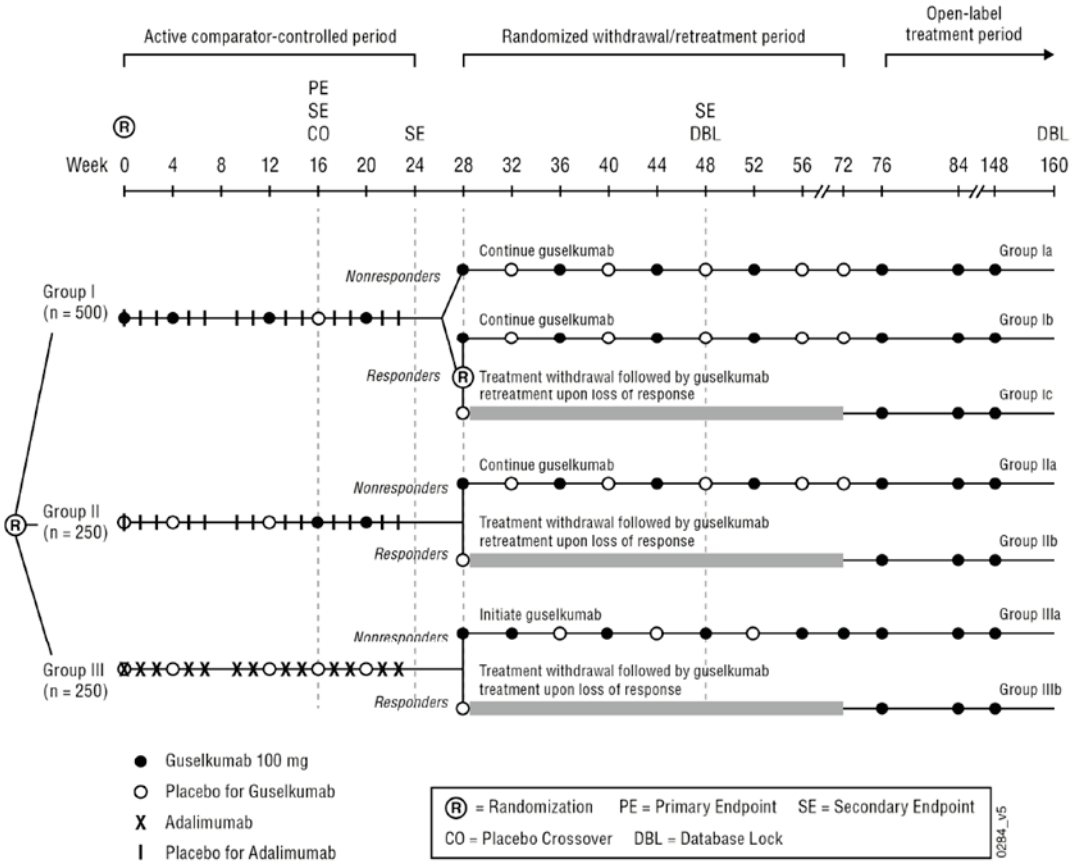
- Subjects were evaluated at screening, baseline (Week 0), and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, and 160.

Figure 6: Schematic Overview of Trial 3001



Source: protocol for Trial 3001

Figure 7: Schematic Overview of Trial 3002



Source: protocol for Trial 3002

For both Trials 3001 and 3002, the protocols specified the following co-primary efficacy endpoints comparing guselkumab to placebo:

- Proportion of subjects achieving an IGA score of 0 (clear) or 1 (minimal) at Week 16
- Proportion of subjects achieving a ≥ 90% improvement in PASI (PASI 90) from baseline at Week 16

Table 17 presents the protocol-specified major secondary efficacy endpoints in Trials 3001 and 3002. Trial 3001 had three major secondary efficacy endpoints related to Week 48, which Trial 3002 did not have due to the difference in trial designs (i.e., Trial 3001 had 48 weeks of continuous treatment for guselkumab and adalimumab). In addition, Trial 3002 had a major secondary efficacy endpoint related to the randomized withdrawal period. It should be noted that all of the major secondary efficacy endpoints presented in Table 17 were included in the pre-specified multiplicity testing strategy (i.e., a sequential gatekeeping approach) to control the Type I error rate.

Table 17: Major Secondary Efficacy Endpoints for Trials 3001 and 3002

Trial 3001	Trial 3002	Endpoint	Comparison
Secondary 1	Secondary 1	IGA score of 0 at Week 24	Superiority to adalimumab
Secondary 2	Secondary 2	IGA score of 0 or 1 at Week 24	Superiority to adalimumab
Secondary 3	Secondary 3	PASI 90 at Week 24	Superiority to adalimumab
NA	Secondary 4	Time to loss of PASI 90 response through Week 48	Superiority to re-randomized placebo
Secondary 4	NA	IGA score of 0 at Week 48	Superiority to adalimumab
Secondary 5	NA	IGA score of 0 or 1 at Week 48	Superiority to adalimumab
Secondary 6	NA	PASI 90 at Week 48	Superiority to adalimumab
Secondary 7	Secondary 5	Change from baseline in DLQI score at Week 16	Superiority to placebo
Secondary 8	Secondary 6	IGA score of 0 or 1 at Week 16	Non-inferiority to adalimumab
Secondary 9	Secondary 7	PASI 75 at Week 16	Non-inferiority to adalimumab
Secondary 10	Secondary 8	PASI 90 at Week 16	Non-inferiority to adalimumab
Secondary 11	Secondary 9	IGA score of 0 or 1 at Week 16	Superiority to adalimumab
Secondary 12	Secondary 10	PASI 75 at Week 16	Superiority to adalimumab
Secondary 13	Secondary 11	PASI 90 at Week 16	Superiority to adalimumab
Secondary 14	Secondary 12	ss-IGA score of 0 or 1 with at least 2-grade improvement from baseline at Week 16	Superiority to placebo
Secondary 15	Secondary 13	Change from baseline in PSSD symptom score at Week 16	Superiority to placebo
Secondary 16	Secondary 14	PSSD symptom score of 0 at Week 24	Superiority to adalimumab

Dermatology Life Quality Index (DLQI); Psoriasis Symptom and Sign Diary (PSSD); Scalp Specific Investigator's Global Assessment (ss-IGA)

The protocols for Trials 3001 and 3002 specified many "other" secondary efficacy endpoints; however, these endpoints were not included in the multiplicity testing strategy. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

Refer to Appendix 13.3 for the scales used to evaluate efficacy.

Dermatology Life Quality Index (DLQI):
According to the protocol, the DLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is a 10-item 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.

Psoriasis Symptom and Sign Diary (PSSD):
The Psoriasis Symptom and Sign Diaries (PSSD) are PRO questionnaires designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit. There are two versions of the PSSD: a 24-hour recall version that asks the subject to answer the questions thinking about the last 24 hours and a 7-day recall version asking the subject to answer the questions thinking about the last 7 days. Both versions of the PSSD are self-administered PRO instruments and include 11 items covering symptoms (itch, pain, stinging, burning and skin tightness) and patient-observable signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) using 0 to 10 numerical rating scales (NRS) for severity. For both the 24-hour and 7-day recall versions, two subscores were derived: the

psoriasis symptom score and the psoriasis sign score. The symptom and sign subscores are calculated by averaging over the 5 symptom items or 6 sign item scores and then converting the average into a 0-100 score (i.e., multiplying the average by 10). A higher score indicates more severe disease.

7.2.1.2. Statistical Methodologies

The protocol-specified primary analysis population was the randomized analysis set, defined as all randomized subjects. This population may also be designated the intent-to-treat (ITT) population. The statistical analysis plans (SAPs) specified conducting supportive analyses using the per-protocol (PP) population, which was specified to include all subjects that were compliant with the protocol. Specifically, the SAPs defined the PP population to be all randomized subjects except those:

- Who did not meet the following inclusion criteria:
  - have a PASI ≥12 at screening and at baseline
  - have an IGA ≥3 at screening and at baseline
  - have an involved BSA ≥10% at screening and at baseline
- Who violated the exclusion diagnosis criteria and previous psoriasis medication criteria specified in the protocol
- Who did not complete the specified exposure to study agent as outlined below
  - subjects randomized to placebo who received guselkumab or adalimumab prior to Week 16
  - subjects randomized to guselkumab at Week 0 but did not receive all scheduled guselkumab administrations or received one or more adalimumab administrations prior to Week 16
  - subjects randomized to adalimumab at Week 0 but did not receive all scheduled adalimumab administrations or received one or more guselkumab administrations prior to Week 16

The SAPs specified pooling investigational sites that enrolled a small number of subjects with sites that enrolled a larger number of subjects by similar region/location so that the number of subjects within the pooled site is at least 20 subjects. The SAPs specified that the pooling decisions were made prior to unblinding.

For the analysis of the co-primary efficacy endpoints (both binary), the protocols specified using the Cochran-Mantel-Haenszel (CMH) test stratified by investigational site (pooled).

For testing for superiority of guselkumab for the binary secondary endpoints, the protocols specified using the CMH test stratified by investigational site (pooled). For testing for superiority of guselkumab for the continuous secondary endpoints, the protocol specified using an analysis of variance (ANOVA) with treatment and investigational site (pooled) as factors in the model. For the secondary endpoint of time to loss of PASI 90 response (Trial 3002), the protocol-specified analysis method was the log-rank test stratified by investigational site (pooled).

For the analyses to test for non-inferiority (all binary endpoints), the protocols specified using a one-sided the (α=0.025) CMH Z-test adjusted by investigator site (pooled). The protocols specified using a non-inferiority margin of 10%, i.e., the lower bound of the 2-sided 95% confidence interval for the difference (guselkumab minus adalimumab) in proportions would need to be greater than -10% to establish non-inferiority.

The protocols specified using a sequential gatekeeping approach to control the Type I error rate. The protocols specified testing the secondary efficacy endpoints in the order presented in Table 17 (see Section 7.2.1.1). The first secondary endpoint will only be tested if the co-primary endpoints are both significant at the 0.05 level, and the subsequent secondary endpoint(s) will be tested only if the current secondary endpoint is significant at the 0.05 level (or the 0.025 level for the non-inferiority comparisons).

Subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The applicant defined this as the "treatment failure criteria." The SAPs specified that baseline values will be assigned for outcomes regardless of the observed data for continuous endpoints, zero will be assigned to improvement and percent change improvement, and non-responder status will be assigned to binary response variables. For the co-primary efficacy endpoints, the SAPs specified conducting sensitivity analyses with the following expanded definitions of the treatment failure criteria:

- Expanded Treatment Failure including Corticosteroid Use: for subjects who received intralesional, topical or systemic corticosteroids prior to Week 16 for any reason, a non-responder status will be assigned after applying treatment failure rules.
- Expanded Treatment Failure including Discontinuation Due to any Adverse Event: the treatment failure criteria will be broadened to include discontinuations of study treatment due to any AE, not limited to AE of worsening of psoriasis.

After the treatment failure criteria is applied, the primary imputation method for the handling of missing data specified in the protocols was the non-responder imputation (NRI) approach for binary endpoints and the last observation carried forward (LOCF) approach for continuous endpoints. For the co-primary efficacy endpoints, the protocols specified the following as sensitivity analyses for the handling of missing data:

- Imputing missing data using LOCF
- Complete case analysis (i.e., missing data not imputed)
- Imputing missing data using the multiple imputation (MI) approach. The details regarding MI were not specified in the protocols or SAPs. For the study report, the applicant imputed the missing data 5 times using a logistic regression model that included treatment group, baseline weight, baseline value (IGA or PASI score), pooled site, and response status from previous visits as factors.

The protocol also specified conducting the above sensitivity analyses for the handling of missing data for secondary efficacy endpoints #1, #2 and #3 listed in Table 17.

7.2.1.3. Patient Disposition, Demographics and Baseline Disease Characteristics

Trial 3001 enrolled and randomized a total of 837 subjects from 101 investigational sites. Trial 3002 enrolled and randomized a total of 992 subjects from 115 investigational sites. Table 18 presents the disposition of subjects during the first 16 weeks of Trials 3001 and 3002. The discontinuation rates were generally similar between the treatment arms within each trial; however, the discontinuation rates were slightly higher in Trial 3002 compared to Trial 3001.

Table 18: Disposition of Subjects through Week 16 for Trials 3001 and 3002

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	Adalimumab (N=334)	Placebo (N=174)	Guselkumab (N=496)	Adalimumab (N=248)	Placebo (N=248)
Discontinued	7 (2%)	10 (3%)	7 (4%)	18 (4%)	11 (4%)	15 (6%)
Adverse Events	4	2	2	9	4	2
Lack of Efficacy	0	1	2	0	2	4
Lost to Follow-up	1	1	1	3	2	1
Withdrawal by Subject	0	4	2	1	0	7
Non-Compliance	2	1	0	1	2	0
Protocol Violation	0	1	0	3	1	1
Other	0	0	0	1	0	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

For both trials, the demographics and baseline disease characteristics are presented in Table 19 and Table 20, respectively. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between each trial. Three subjects randomized to the adalimumab arm in Trial 3001 and one subject randomized to the guselkumab arm in Trial 3002 had a baseline IGA score of 2 (mild); therefore, these subjects did not meet the baseline inclusion criterion for IGA.

Table 19: Demographics for Trials 3001 and 3002

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	Adalimumab (N=334)	Placebo (N=174)	Guselkumab (N=496)	Adalimumab (N=248)	Placebo (N=248)
Age (years)						
Mean (SD)	44 (13)	43 (13)	45 (13)	44 (12)	43 (12)	43 (12)
Median	43	43	45	44	43	43
Range	19 – 76	18 – 87	19 – 77	18 – 74	19 – 70	18 – 71
18-64	311 (95%)	318 (95%)	164 (94%)	473 (95%)	237 (96%)	239 (96%)
≥ 65	18 (5%)	16 (5%)	10 (6%)	23 (5%)	11 (4%)	9 (4%)
Sex						
Male	240 (73%)	249 (75%)	119 (68%)	349 (70%)	170 (69%)	173 (70%)
Female	89 (27%)	85 (25%)	55 (32%)	147 (30%)	78 (31%)	75 (30%)
Race						
White	262 (80%)	277 (83%)	145 (83%)	408 (82%)	200 (81%)	206 (83%)
Black	6 (2%)	8 (2%)	3 (2%)	6 (1%)	5 (2%)	8 (3%)
Asian	51 (15%)	47 (14%)	23 (13%)	72 (15%)	37 (15%)	27 (11%)
Other	10 (3%)	2 (1%)	3 (2%)	10 (2%)	6 (2%)	7 (3%)
Weight (kg)[1]						
Mean (SD)	89.5 (20.1)	90.5 (21.8)	88.0 (24.4)	89.6 (20.8)	87.6 (21.0)	88.6 (20.0)
Median	87.1	87.1	83.0	87.7	84.6	85.6
Range	48 – 161	41 – 173.6	47.8 – 169	44.9 – 198	44.5 – 174.6	52 – 163.3
≤ 90 kg	189 (57%)	191 (57%)	111 (64%)	277 (56%)	153 (62%)	141 (57%)
> 90 kg	140 (43%)	142 (43%)	63 (36%)	219 (44%)	94 (38%)	107 (43%)
Country						
US	65 (20%)	67 (20%)	38 (22%)	93 (19%)	48 (19%)	49 (20%)
Non-US	264 (80%)	267 (80%)	136 (77%)	403 (81%)	200 (81%)	199 (80%)
Region						
North America[2]	115 (35%)	115 (34%)	62 (36%)	160 (32%)	81 (33%)	79 (32%)
All Other	214 (65%)	219 (66%)	112 (64%)	336 (68%)	167 (67%)	169 (68%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.
(1) In both trials, one subject randomized to adalimumab had missing baseline weight.
(2) United States and Canada

Table 20: Baseline Disease Characteristics for Trials 3001 and 3002

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	**Adalimumab (N=334)**	**Placebo (N=174)**	**Guselkumab (N=496)**	**Adalimumab (N=248)**	**Placebo (N=248)**
IGA						
2 - Mild	0	3 (1%)	0	1 (<1%)	0	0
3 - Moderate	252 (77%)	241 (72%)	131 (75%)	380 (77%)	195 (79%)	191 (77%)
4 - Severe	77 (23%)	90 (27%)	43 (25%)	115 (23%)	53 (21%)	57 (23%)
PASI						
Mean (SD)	22.1 (9.5)	22.4 (9.0)	20.4 (8.7)	21.9 (8.8)	21.7 (9.0)	21.5 (8.0)
Median	18.6	20.0	17.4	19.2	19.0	19.0
Range	12 – 68.4	7 – 58	12 – 61	11.7 – 64.9	11.7 – 58	12 – 50.9
Percent BSA						
Mean (SD)	28.3 (17.1)	28.6 (16.7)	25.8 (15.9)	28.5 (16.4)	29.1 (16.7)	28.0 (16.5)
Median	22.0	23.0	20.0	24.0	25.0	22.0
Range	10 – 90	10 – 85	10 – 85	10 – 92	10 – 86	10 – 89

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

7.2.1.4. Results for the Co-Primary Efficacy Endpoints

Table 21 presents the results for the co-primary efficacy endpoints at Week 16 for Trials 3001 and 3002. Guselkumab was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials. The results for the ITT and PP populations were very similar.

Table 21: Results for the Co-Primary Efficacy Endpoints at Week 16

	Trial 3001			Trial 3002		
	Guselkumab	**Placebo**	**P-value(3)**	**Guselkumab**	**Placebo**	**P-Value(3)**
ITT(1)	N=329	N=174		N=496	N=248	
IGA score of 0 or 1	280 (85%)	12 (7%)	<0.001	417 (84%)	21 (8%)	<0.001
PASI 90	241 (73%)	5 (3%)	<0.001	347 (70%)	6 (2%)	<0.001
PP(2)	N=317	N=174		N=469	N=246	
IGA score of 0 or 1	276 (87%)	12 (7%)	<0.001	403 (86%)	21 (9%)	<0.001
PASI 90	238 (75%)	5 (3%)	<0.001	336 (72%)	6 (2%)	<0.001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) Intent-to-Treat (ITT) population: all randomized subjects. Missing data was imputed using non-responder imputation (NRI).
(2) Per-Protocol (PP) population (see Section 7.2.1.2)
(3) P-value based on a CMH test stratified by investigational site (pooled).

Table 22 presents the number of subjects with missing data for the co-primary efficacy endpoints by week, treatment arm, and trial. Overall, the proportion of subjects with missing data was relatively low. In both trials, the proportion of subjects with missing data for Week 16 (i.e., primary efficacy timepoint) was slightly higher in the placebo arm compared to the guselkumab arm. In addition, the proportion of subjects with missing data for Week 16 was slightly higher in Trial 3002 compared to Trial 3001.

Table 22: Missing Data for the Co-Primary Efficacy Endpoints by Week

	Trial 3001		Trial 3002	
	Guselkumab (N=329)	Placebo (N=174)	Guselkumab (N=496)	Placebo (N=248)
Baseline	0	0	0	0
Week 2	1 (0.3%)	3 (1.7%)	6 (1.2%)	2 (0.8%)
Week 4	2 (0.6%)	3 (1.7%)	6 (1.2%)	4 (1.6%)
Week 8	4 (1.2%)	3 (1.7%)	8 (1.6%)	5 (2.0%)
Week 12	3 (0.9%)	4 (2.3%)	9 (1.8%)	8 (3.2%)
Week 16	6 (1.8%)	6 (3.4%)	12 (2.4%)	11 (4.4%)

Source: Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects.

The primary method of handling missing data specified in the protocol was non-responder imputation (NRI). The protocol specified the following three sensitivity analyses for the handling of missing data: (i) impute missing data using LOCF, (ii) complete case analysis (i.e., missing data is not imputed), and (iii) impute missing data using multiple imputation (MI). This reviewer conducted an additional sensitivity analysis under the worst case scenario (i.e., missing data for guselkumab is imputed as non-responders and missing data for placebo is imputed as responders). Table 23 presents the results for the co-primary efficacy endpoints in both trials by the various imputation methods. For both trials, the results were very similar across the various methods. In the extreme case (i.e., worst case scenario), guselkumab remained statistically significant to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials.

Table 23: Results for Co-Primary Efficacy Endpoints at Week 16 with Different Approaches for Handling Missing Data

Endpoint	Trial 3001		Trial 3002	
	Guselkumab (N=329)	Placebo (N=174)	Guselkumab (N=496)	Placebo (N=248)
IGA score of 0 or 1				
NRI (Primary)	85%	7%	84%	8%
LOCF(1)	87%	7%	85%	9%
Observed Cases	87%	7%	86%	9%
MI(2)	86%	8%	86%	10%
Worst Case(3)	85%	10%	84%	13%
PASI 90				
NRI (Primary)	73%	3%	70%	2%
LOCF(1)	74%	3%	71%	2%
Observed Cases	75%	3%	72%	3%
MI(2)	75%	4%	72%	3%
Worst Case(3)	73%	6%	70%	7%

Source: Statistical Reviewer's Analysis (NRI, LOCF, MI and Observed Cases same as Applicant's Analysis)
(1) Missing data imputed using the last observation carried forward (LOCF).
(2) Multiple Imputation (MI): missing data was imputed using a logistic regression model that included treatment group, baseline weight, baseline value (IGA or PASI score), pooled site, and response status from previous visits as factors. The values displayed are the average of the 5 imputed datasets.
(3) Missing data for guselkumab is imputed as non-responders and missing data for placebo is imputed as responders.

It should be noted that subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis were considered treatment failures for the efficacy analyses. The applicant defined this as the "treatment failure criteria." For the co-primary efficacy

endpoints, the SAPs specified conducting sensitivity analyses with the following expanded definitions of the treatment failure criteria:

- Expanded Treatment Failure including Corticosteroid Use: for subjects who received intralesional, topical or systemic corticosteroids prior to Week 16 for any reason, a non-responder status will be assigned after applying treatment failure rules.
- Expanded Treatment Failure including Discontinuation Due to any Adverse Event: the treatment failure criteria will be broadened to include discontinuations of study treatment due to any AE, not limited to AE of worsening of psoriasis.

Table 24 presents the results for the co-primary efficacy endpoints at Week 16 under the different definitions of the treatment failure criteria. After applying the treatment failure criteria, missing data was imputed as non-responders. In both trials, the results for the various definitions were almost identical to each other.

Table 24: Results for Co-Primary Efficacy Endpoints at Week 16 with Different Definitions of the Treatment Failure Criteria

	Trial 3001		Trial 3002	
Endpoint	**Guselkumab (N=329)**	**Placebo (N=174)**	**Guselkumab (N=496)**	**Placebo (N=248)**
IGA score of 0 or 1				
TFC[(1)]	85%	7%	84%	8%
TFC + Corticosteroid Use[(2)]	84%	7%	83%	8%
TFC + Discontinued due to any AE[(3)]	85%	7%	83%	8%
PASI 90				
TFC[(1)]	73%	3%	70%	2%
TFC + Corticosteroid Use[(2)]	72%	3%	69%	2%
TFC + Discontinued due to any AE[(3)]	73%	3%	69%	2%

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

(1) Treatment Failure Criteria (TFC): subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures.
(2) Subjects who received intralesional, topical or systemic corticosteroids prior to Week 16 for any reason are considered treatment failures.
(3) The treatment failure criteria are broadened to include discontinuations of study treatment due to any AE, not limited to AE of worsening of psoriasis.

7.2.1.5. Results for the Secondary Efficacy Endpoints

This section summarizes the results for the investigator reported major secondary efficacy endpoints. Section 7.2.1.6 summarizes the results for the major secondary efficacy endpoints based on patient reported outcomes (PROs).

Trials 3001 and 3002 included adalimumab as an active comparator. In both trials, all subjects randomized to adalimumab in the North American sites (i.e., U.S. and Canada) received U.S. licensed Humira (adalimumab). Subjects randomized to adalimumab at all other sites received EU approved adalimumab. As the applicant did not provide an adequate scientific bridge between U.S. licensed Humira and EU approved adalimumab, these products are considered distinct products for the purpose of this review.

Table 25 presents the results for the investigator reported major secondary efficacy endpoints against adalimumab in the overall population (i.e., all sites) and by region (i.e., North America vs. All Other) for Trials 3001 and 3002. In both trials, guselkumab was statistically superior to adalimumab (p-values < 0.001) in the overall population for all of the major secondary efficacy endpoints presented in Table 25. In addition, guselkumab was statistically superior to adalimumab (p-values ≤ 0.027) in the North American subgroup (i.e., the sites that used US licensed Humira).

To evaluate the impact of treatment with guselkumab on psoriasis located on the scalp, the applicant included a secondary efficacy endpoint based on the Scalp Specific Investigator's Global Assessment (ss-IGA) scale, see Table 47 in Appendix 13.3. Specifically, the applicant evaluated the proportion of subjects with an ss-IGA score of 0 or 1 with at least a 2-grade improvement from baseline at Week 16 for guselkumab compared to placebo. This analysis was prespecified to include only subjects with a baseline ss-IGA score ≥ 2 (mild) and the results are presented in Table 26. Approximately 84% and 82% of subjects had an ss-IGA score ≥ 2 at baseline and were included in the analysis for Trials 3001 and 3002, respectively. In both trials, guselkumab was statistically superior to placebo (p-values < 0.001) for this endpoint at Week 16.

Table 25: Results for the Investigator Reported Secondary Efficacy Endpoints Against Adalimumab

	Trial 3001			Trial 3002		
Endpoint	**Guselkumab (N=329)**	**Adalimumab (N=334)**	**P-Value[1]**	**Guselkumab (N=496)**	**Adalimumab (N=248)**	**P-Value[1]**
IGA score of 0 at Week 24	*173 (53%)*	*98 (29%)*	*<0.001*	*257 (52%)*	*78 (31%)*	*<0.001*
North America[2]	61 (53%)	27 (23%)	<0.001	76 (48%)	23 (28%)	0.005
All Other[3,4]	112 (52%)	71 (32%)	<0.001	181 (54%)	55 (33%)	<0.001
IGA score of 0 or 1 at Week 24	277 (84%)	205 (61%)*	<0.001	414 (83%)	161 (65%)	<0.001
North America[2]	97 (84%)	62 (54%)	<0.001	119 (74%)	46 (57%)	0.005
All Other[3,4]	180 (84%)	143 (65%)*	<0.001	295 (88%)	115 (69%)	<0.001
PASI 90 at Week 24	*264 (80%)*	*177 (53%)*	*<0.001*	*373 (75%)*	*136 (55%)*	*<0.001*
North America[2]	92 (80%)	51 (44%)	<0.001	113 (71%)	41 (51%)	0.003
All Other[3,4]	172 (80%)	126 (58%)	<0.001	260 (77%)	95 (57%)	<0.001
IGA score of 0 at Week 48	*166 (50%)*	*86 (26%)*	*<0.001*	--	--	--
North America[2]	54 (47%)	28 (24%)	<0.001	--	--	--
All Other[3,4]	112 (52%)	58 (26%)	<0.001	--	--	--
IGA score of 0 or 1 at Week 48	*265 (81%)*	*184 (55%)**	*<0.001*	--	--	--
North America[2]	91 (79%)	62 (54%)	<0.001	--	--	--
All Other[3,4]	174 (81%)	122 (56%)*	<0.001	--	--	--
PASI 90 at Week 48	*251 (76%)*	*160 (48%)*	*<0.001*	--	--	--
North America[2]	84 (73%)	53 (46%)	<0.001	--	--	--
All Other[3,4]	167 (78%)	107 (49%)	<0.001	--	--	--
IGA score of 0 or 1 at Week 16	*280 (85%)*	*219 (66%)**	*<0.001*	*417 (84%)*	*168 (68%)*	*<0.001*
North America[2]	97 (84%)	70 (61%)	<0.001	119 (74%)	50 (62%)	0.027
All Other[3,4]	183 (86%)	149 (68%)*	<0.001	298 (89%)	118 (71%)	<0.001
PASI 75 at Week 16	*300 (91%)*	*244 (73%)*	*<0.001*	*428 (86%)*	*170 (69%)*	*<0.001*
North America[2]	105 (91%)	80 (70%)	<0.001	132 (83%)	51 (63%)	<0.001
All Other[3,4]	195 (91%)	164 (75%)	<0.001	296 (88%)	119 (71%)	<0.001
PASI 90 at Week 16	*241 (73%)*	*166 (50%)*	*<0.001*	*347 (70%)*	*116 (47%)*	*<0.001*
North America[2]	84 (73%)	47 (41%)	<0.001	102 (64%)	34 (42%)	<0.001
All Other[3,4]	157 (73%)	119 (54%)	<0.001	245 (73%)	82 (49%)	<0.001

Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using non-responder imputation (NRI).
(1) P-value based on a CMH test stratified by investigational site (pooled).
(2) US and Canada. Sample sizes for Trial 3001 = (N_G, N_A, N_P) = (115, 115, 62) and for Trial 3002 = (N_G, N_A, N_P) = (160, 81, 79).
(3) Trial 3001: Australia, Germany, Hungary, Poland, Russia, Spain, South Korea and Taiwan. Sample sizes for Trial 3001 = (N_G, N_A, N_P) = (214, 219, 112).
(4) Trial 3002: Australia, Czech Republic, Germany, Poland, Russian, Spain and Sou h Korea. Sample sizes for Trial 3002 = (N_G, N_A, N_P) = (336, 167, 169).
*Three subjects in the adalimumab arm had a baseline IGA score of 2. In the applicant's analysis, one of hese subjects was considered a success with an IGA score of 1; however, for this table, this subject was considered a failure.

Table 26: Results for Psoriasis Involving the Scalp Against Placebo

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	**Placebo (N=174)**	**P-Value[1]**	**Guselkumab (N=496)**	**Placebo (N=248)**	**P-Value[1]**
Baseline ss-IGA						
0 – Absence	38 (12%)	24 (14%)		73 (15%)	36 (15%)	
1 – Mild	14 (4%)	5 (3%)		15 (3%)	10 (4%)	
2 – Very Mild	49 (15%)	31 (18%)		80 (16%)	33 (13%)	
3 – Moderate	171 (52%)	89 (51%)		267 (54%)	133 (54%)	
4 – Severe	57 (17%)	25 (14%)		61 (12%)	36 (15%)	
ss-IGA score of 0 or 1 with at least 2-grade improvement from baseline at Week 16	231/277 (83%)	21/145 (14%)	<0.001	329/408 (81%)	22/202 (11%)	<0.001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) P-value based on a CMH test stratified by investigational site (pooled). Analysis based on subjects with an ss-IGA score ≥ 2.

7.2.1.6. Patient Reported Outcomes (PROs)

The protocols specified three major secondary efficacy endpoints based on patient reported outcomes (PROs). One of these endpoints was based on the Dermatology Life Quality Index (DLQI). In an advice letter dated October 14, 2014, the Agency stated that the DLQI is not a well-defined and reliable instrument because it does not measure any specific concept. In addition, the Agency stated that the DLQI may be useful as an exploratory endpoint but not to support labeling claims. Therefore, the results for DLQI are not presented in this review.

For both trials, the protocols specified the following two major secondary efficacy endpoints based on the Psoriasis Symptom and Sign Diary (PSSD):

- Absolute change from baseline in PSSD symptom score at Week 16 [guselkumab vs. placebo for superiority]
- Proportion of subjects with a PSSD symptom score of 0 at Week 24 [guselkumab vs. adalimumab for superiority]

The PSSD data was collected using an electronic device (ePRO/eDiary/LogPad). Approximately 22% and 18% of randomized subjects had missing baseline PSSD scores in Trials 3001 and 3002, respectively. The applicant stated that this was due to technical difficulties associated with the device itself and with data transmission. Subjects with missing baseline PSSD scores were not included in the analysis.

Table 27 presents the results for the absolute change from baseline in PSSD symptom score to Week 16 for guselkumab against placebo. In both trials, guselkumab was statistically superior to placebo (p-values < 0.001) for this endpoint.

Table 27: Absolute Change from Baseline in PSSD Symptom Score to Week 16

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	Placebo (N=174)	P-value[1]	Guselkumab (N=496)	Placebo (N=248)	P-Value[1]
Baseline PSSD symptom score						
N[2]	249	129		411	198	
Mean (SD)	54.4 (24.6)	48.3 (23.8)		54.2 (26.2)	58.6 (23.5)	
Median	56.0	46.0		54.0	60.0	
Range	0 to 100	4 to 100		0 to 100	12 to 100	
Change from baseline in PSSD symptom score to Week 16						
N[3]	249	129		411	198	
Mean (SD)	-41.9 (24.6)	-3.0 (19.6)	<0.001	-40.4 (26.5)	-8.3 (23.7)	<0.001
Median	-40.0	-2.0		-38.0	-8.0	
Range	-96 to 12	-60 to 60		-100 to 34	-88 to 64	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) P-value based on an ANOVA model with treatment and investigational site (pooled) as factors in the model.
(2) Subjects with baseline PSSD scores.
(3) Subjects with baseline PSSD scores. Missing data was imputed using the last observation carried forward (LOCF).

Table 28 presents the results for the proportion of subjects with a PSSD symptom score of 0 at Week 24 for guselkumab against adalimumab. In both trials, guselkumab was statistically superior to adalimumab (p-values ≤ 0.001) in the overall population (i.e., all sites). For the North American subgroup (i.e., sites that used U.S. licensed adalimumab), guselkumab was statistically superior to adalimumab (p-value = 0.010) in Trial 3002; however, guselkumab was not statistically superior to adalimumab (p-value = 0.063) in Trial 3001. This was primarily due to a decrease in sample size for the North American subgroup.

Table 28: Proportion of Subjects with a PSSD Symptom Score of 0 at Week 24

	Trial 3001			Trial 3002		
	Guselkumab (N=329)	Adalimumab (N=334)	P-Value[1]	Guselkumab (N=496)	Adalimumab (N=248)	P-Value[1]
N[2]	248	273		410	200	
Overall	90 (36%)	59 (22%)	<0.001	144 (35%)	45 (23%)	0.001
North America[3]	36 (37%)	25 (26%)	0.063	60 (43%)	18 (25%)	0.010
All Other[4,5]	54 (36%)	34 (20%)	<0.001	84 (31%)	27 (21%)	0.031

Source: Statistical Reviewer's Analysis
(1) P-value based on a CMH test stratified by investigational site (pooled).
(2) Subjects with a baseline PSSD symptom score > 0. Missing data was imputed using last observation carried forward (LOCF).
(3) US and Canada. Sample sizes for Trial 3001 = (N_G, N_A) = (97, 102) and for Trial 3002 = (N_G, N_A) = (138, 73).
(4) Trial 3001: Australia, Germany, Hungary, Poland, Russia, Spain, South Korea and Taiwan. Sample sizes for Trial 3001 = (N_G, N_A) = (151, 171).
(5) Trial 3002: Australia, Czech Republic, Germany, Poland, Russian, Spain and South Korea. Sample sizes for Trial 3002 = (N_G, N_A) = (272, 127).

In an advice letter dated February 22, 2016, the Agency stated that it is not clear whether it is appropriate to average over the five symptom items (i.e., itch, pain, stinging, burning, and skin tightness). In addition, the Agency stated that it is not clear whether absolute change or at least a 1-point change on the PSSD symptom score is clinically meaningful. Therefore, the Agency recommended the applicant propose clinically meaningful responder definitions for the individual

symptom items. Based on the advice letter, the applicant included responder definitions at Week 16 for the five symptom items as "other" secondary efficacy endpoints, which were not included in the multiplicity testing procedure. The applicant specified a 4-point threshold for itch, pain, burning and skin tightness. The applicant specified a 3-point threshold for stinging. The results for these responder definitions at Week 16 are presented in Table 29. In both trials, there was a large treatment effect for each PSSD symptom item and the nominal p-values were all <0.001 for the comparison of guselkumab to placebo.

Table 29: Responder Analysis for PSSD Symptom Items at Week 16

	Trial 3001		Trial 3002	
PSSD Symptom	**Guselkumab (N=329)**	**Placebo (N=174)**	**Guselkumab (N=496)**	**Placebo (N=248)**
Itch				
N[1]	217	105	349	183
≥4-point reduction	163 (75%)	6 (6%)	269 (77%)	29 (16%)
Skin Tightness				
N[1]	205	98	243	170
≥4-point reduction	163 (80%)	8 (8%)	243 (76%)	33 (19%)
Burning				
N[1]	158	85	267	145
≥4-point reduction	127 (80%)	8 (11%)	212 (79%)	31 (21%)
Stinging				
N[1]	184	85	279	151
≥3-point reduction	152 (83%)	15 (18%)	235 (84%)	41 (27%)
Pain				
N[1]	174	82	282	146
≥4-point reduction	132 (76%)	10 (12%)	213 (76%)	27 (18%)

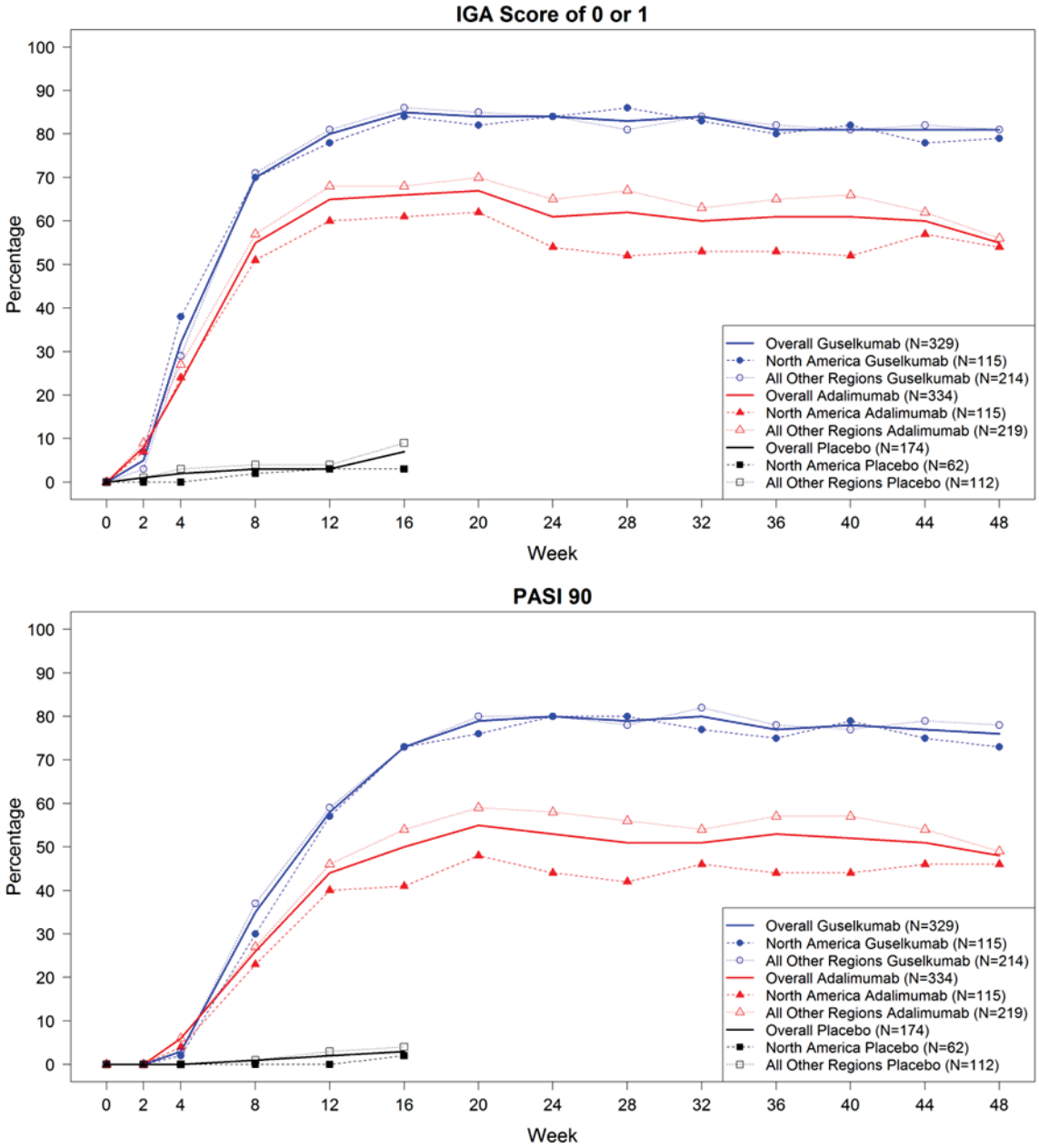
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) For itch, skin tightness, burning, and pain, N is the number of subjects with a baseline item score ≥ 4. For stinging, N is the number of subjects with a baseline item score ≥ 3. Missing data was imputed using the last observation carried forward (LOCF).

The full Evidence Dossier, which was submitted to support the development of the PSSD, was reviewed by the Clinical Outcome Assessment (COA) review team. Dr. Yasmin Choudhry, concluded that based on the applicant's qualitative and quantitative evidence presented in the Evidence Dossier, the PSSD Symptom domain appropriately measures symptom severity and appears to be fit for purpose for the drug development program (review dated 4/8/2017 by Yasmin Choudhry). Qualitative data supports the importance and relevance of these symptoms from the patient's perspective.

7.2.1.7. Efficacy Over Time

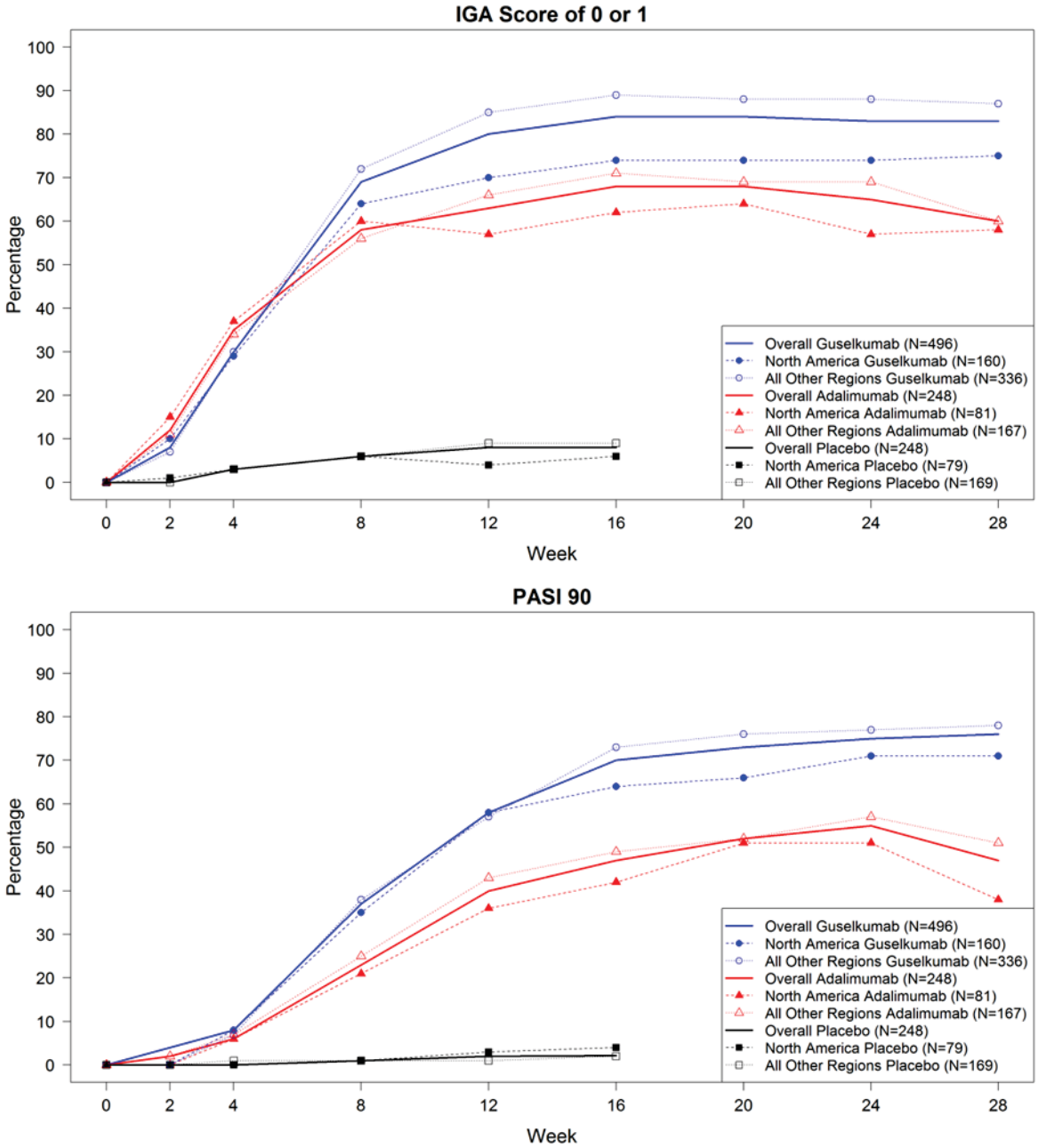
Figure 8 presents the results for IGA score of 0 or 1 and PASI 90 through Week 48 for Trial 3001. Figure 9 presents the results for IGA score of 0 or 1 and PASI 90 through Week 28 for Trial 3002.

Figure 8: Results for IGA Score of 0 or 1 and PASI 90 Through Week 48 for Trial 3001



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using non-responder imputation (NRI).

Figure 9: Results for IGA Score of 0 or 1 and PASI 90 Through Week 28 for Trial 3002

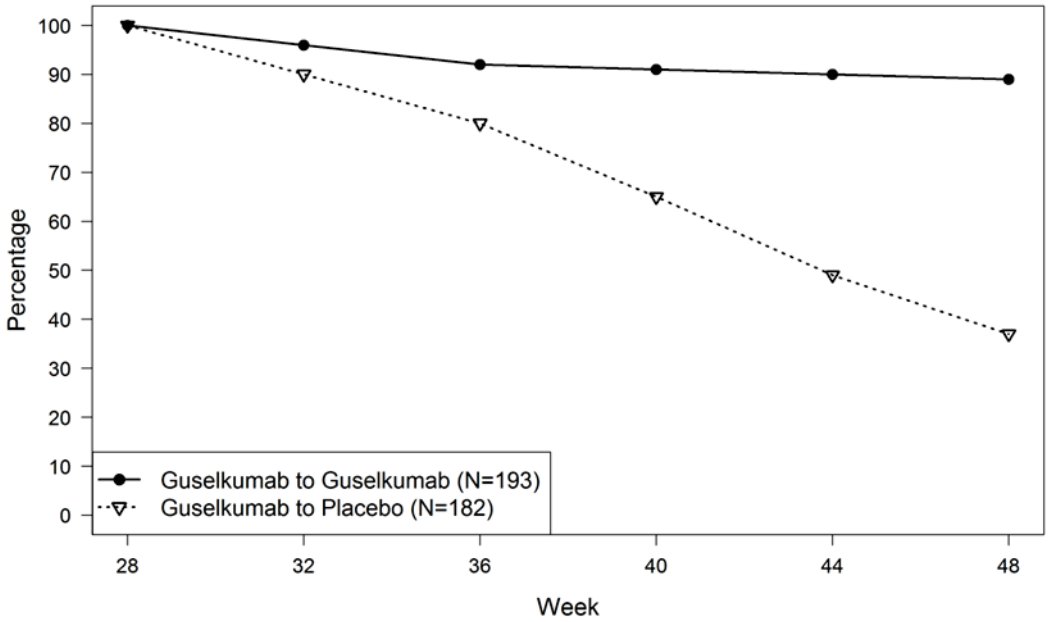


Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using non-responder imputation (NRI).

Trial 3002 evaluated maintenance of efficacy for an additional 20 weeks (Weeks 28 to 48). Subjects randomized to guselkumab at Week 0 and who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with guselkumab or be withdrawn from therapy (i.e., placebo). At Week 48, 89% of subjects who continued on guselkumab were PASI 90 responders compared to 37% of subjects who were withdrawn from therapy. For responders at Week 28 who were re-randomized to treatment withdrawal, the median time to loss of PASI 90 was approximately 15 weeks. Figure 10 presents the PASI 90 response rates during the

maintenance period (Weeks 28 to 48) for the re-randomized subjects (i.e., continue guselkumab or switch to placebo).

Figure 10: PASI 90 Response for the Maintenance Period (Weeks 28 to 48) for Trial 3002



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); PASI 90 responders re-randomized at Week 28; Missing data imputed using non-responder imputation (NRI).

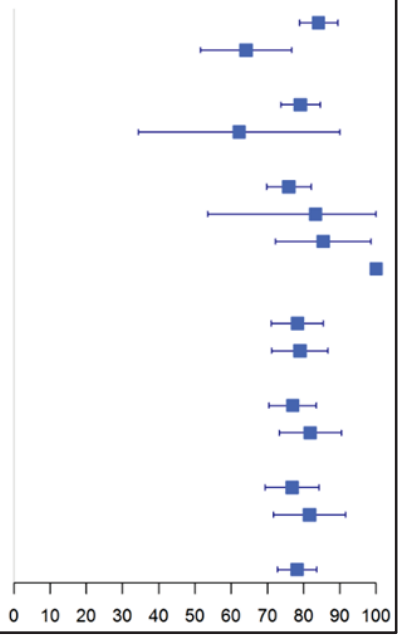
7.2.1.8. Findings in Special/Subgroup Populations

7.2.1.8.1. Gender, Race, Age, Weight, Baseline Disease Severity and Prior Use of Systemic Therapy

Figure 11 and Figure 12 present the results for the co-primary efficacy endpoints (i.e., IGA score of 0 or 1 at Week 16 and PASI 90 at Week 16) by gender, age (18-64 and 65+ years), race (White, Black, Asian, and Other), weight (≤90 kg and >90 kg), baseline IGA score, and prior use of systemic therapy for Trial 3001. The same results for Trial 3002 are presented in Figure 13 and Figure 14. For gender, the treatment effect was larger in males compared to females for IGA score of 0 or 1 in both trials; however, this is due to a larger placebo response rate in females compared to males. For PASI 90, the treatment effect was larger in males in Trial 3001; however, the treatment effect was larger in females in Trial 3002. Approximately 94% and 96% of subjects were 18 to 64 years of age in Trials 3001 and 3002, respectively; therefore, it would be difficult to detect any differences in efficacy between this subgroup and its complement (i.e., ≥ 65 years). For race, the treatment effect was generally consistent; however, it should be noted that the sample size for some of the non-White subgroups (i.e., Black and Other) were relatively small. In both trials, the treatment effect on IGA score of 0 or 1 was consistent across the two weight subgroups (≤90 kg and >90 kg); however, for PASI 90, the treatment effect was larger in the ≤90 kg subgroup in both trials. The treatment effect was generally consistent across the baseline IGA score subgroups and the prior use of systemic therapy subgroups.

Figure 11: IGA Score of 0 or 1 at Week 16 by Gender, Age, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for Trial 3001

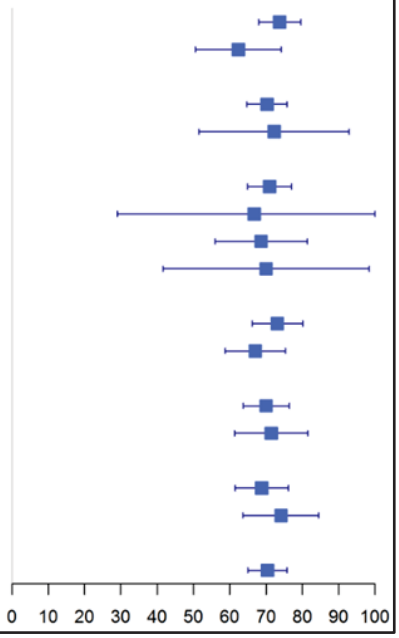
Subgroups (n[G], n[P])	Guselkumab (N=329)	Placebo (N=174)	Difference
Gender			
Males (240, 119)	87.5%	3.4%	84.1%
Females (89, 55)	78.7%	14.5%	64.1%
Age			
18-64 (311, 164)	85.9%	6.7%	79.1%
65+ (18, 10)	72.2%	10.0%	62.2%
Race			
White (262, 145)	82.8%	6.9%	75.9%
Black (6, 3)	83.3%	0%	83.3%
Asian (51, 23)	94.1%	8.7%	85.4%
Other (10, 3)	100%	0%	100%
Baseline Weight			
<=90 kg (189, 111)	87.3%	9.0%	78.3%
>90 kg (140, 63)	82.1%	3.2%	79.0%
Baseline IGA			
3 - Moderate (252, 131)	86.1%	9.2%	77.0%
4 - Severe (77, 43)	81.8%	0%	81.8%
Prior Systemic Therapy			
Yes (229, 106)	83.4%	6.6%	76.8%
No (100, 68)	89.0%	7.4%	81.6%
Overall	85.1%	6.9%	78.2%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 12: PASI 90 Response at Week 16 by Gender, Age, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for Trial 3001

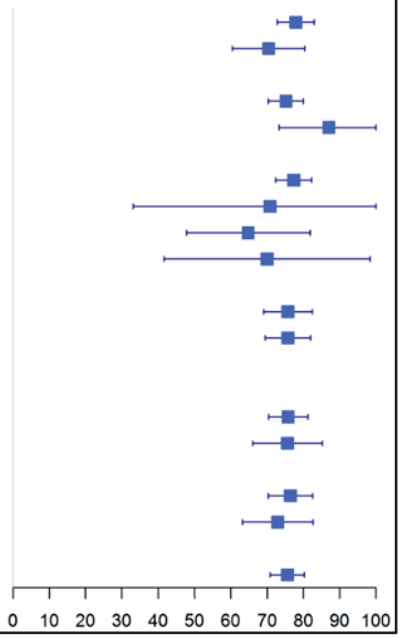
Subgroups (n[G], n[P])	Guselkumab (N=329)	Placebo (N=174)	Difference
Gender			
Males (240, 119)	74.6%	0.8%	73.7%
Females (89, 55)	69.7%	7.3%	62.4%
Age			
18-64 (311, 164)	73.3%	3.0%	70.3%
65+ (18, 10)	72.2%	0%	72.2%
Race			
White (262, 145)	74.4%	3.4%	71.0%
Black (6, 3)	66.7%	0%	66.7%
Asian (51, 23)	68.6%	0%	68.6%
Other (10, 3)	70.0%	0%	70.0%
Baseline Weight			
<=90 kg (189, 111)	76.7%	3.6%	73.1%
>90 kg (140, 63)	68.6%	1.6%	67.0%
Baseline IGA			
3 - Moderate (252, 131)	73.8%	3.8%	70.0%
4 - Severe (77, 43)	71.4%	0%	71.4%
Prior Systemic Therapy			
Yes (229, 106)	71.6%	2.8%	68.8%
No (100, 68)	77.0%	2.9%	74.1%
Overall	73.3%	2.9%	70.4%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 13: IGA Score of 0 or 1 at Week 16 by Gender, Age, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for Trial 3002

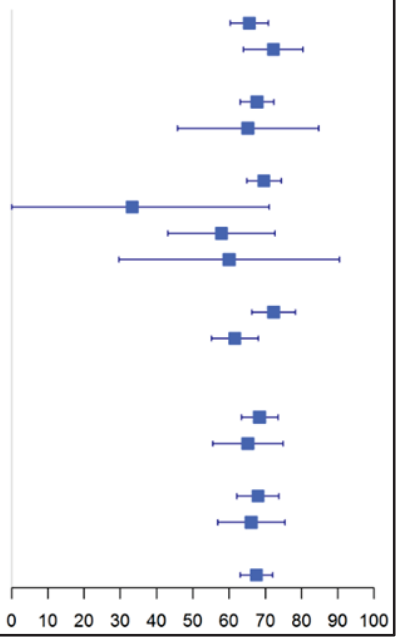
Subgroups (n[G], n[P])	Guselkumab (N=496)	Placebo (N=248)	Difference
Gender			
Males (349, 173)	83.1%	5.2%	77.9%
Females (147, 75)	86.4%	16.0%	70.4%
Age			
18-64 (473, 239)	83.9%	8.8%	75.2%
65+ (23, 9)	87.0%	0%	87.0%
Race			
White (408, 206)	84.6%	7.3%	77.3%
Black (6, 8)	83.3%	12.5%	70.8%
Asian (72, 27)	83.3%	18.5%	64.8%
Other (10, 27)	70.0%	0%	70.0%
Baseline Weight			
<=90 kg (277, 141)	88.4%	12.8%	75.7%
>90 kg (219, 107)	78.5%	2.8%	75.7%
Baseline IGA			
2 - Mild (1, 0)	0%	NA	NA
3 - Moderate (380, 191)	84.7%	8.9%	75.8%
4 - Severe (115, 57)	82.6%	7.0%	75.6%
Prior Systemic Therapy			
Yes (361, 169)	85.9%	9.5%	76.4%
No (135, 79)	79.3%	6.3%	72.9%
Overall	84.1%	8.5%	75.6%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 14: PASI 90 Response at Week 16 by Gender, Age, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for Trial 3002

Subgroups (n[G], n[P])	Guselkumab (N=496)	Placebo (N=248)	Difference
Gender			
Males (349, 173)	67.3%	1.7%	65.6%
Females (147, 75)	76.2%	4.0%	72.2%
Age			
18-64 (473, 239)	70.2%	2.5%	67.7%
65+ (23, 9)	65.2%	0%	65.2%
Race			
White (408, 206)	71.6%	1.9%	69.6%
Black (6, 8)	33.3%	0%	33.3%
Asian (72, 27)	65.3%	7.4%	57.9%
Other (10, 27)	60.0%	0%	60.0%
Baseline Weight			
<=90 kg (277, 141)	76.5%	4.3%	72.3%
>90 kg (219, 107)	61.6%	0%	61.6%
Baseline IGA			
2 - Mild (1, 0)	0%	NA	NA
3 - Moderate (380, 191)	70.5%	2.1%	68.4%
4 - Severe (115, 57)	68.7%	3.5%	65.2%
Prior Systemic Therapy			
Yes (361, 169)	70.9%	3.0%	68.0%
No (135, 79)	67.4%	1.3%	66.1%
Overall	70.0%	2.4%	67.5%



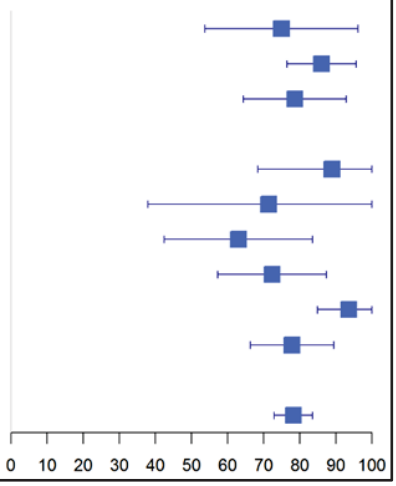
Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

7.2.1.8.2. Geographic Location (Country)

Trial 3001 was conducted in 10 countries (i.e., Australia, Canada, Germany, Spain, Hungary, South Korea, Poland, Russia, Taiwan, and United States) and Trial 3002 was conducted in 9 countries (i.e., Australia, Canada, Germany, Spain, South Korea, Poland, Czech Republic, Russia, and United States). Figure 15 and Figure 16 present the results for the co-primary efficacy endpoints (i.e., IGA score of 0 or 1 at Week 16 and PASI 90 at Week 16) by country for Trial 3001. The same results for Trial 3002 are presented in Figure 17 and Figure 18. In both trials, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

Figure 15: IGA Score of 0 or 1 at Week 16 by Country for Trial 3001

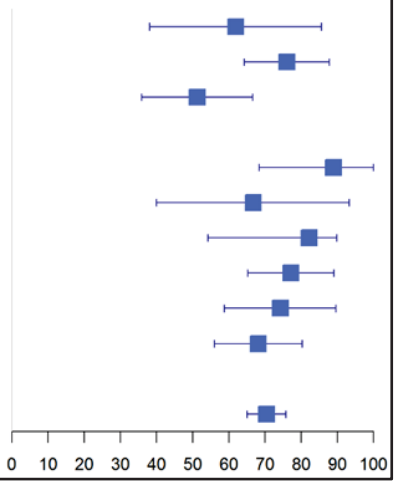
Subgroups (n[G], n[P])	Guselkumab (N=329)	Placebo (N=174)	Difference
Country			
Australia (23, 13)	82.6%	7.7%	74.9%
Canada (50, 24)	86.0%	0%	86.0%
Germany (41, 23)	82.9%	4.3%	78.6%
Spain (8, 4)	100%	0%	100%
Hungary (9, 7)	88.9%	0%	88.9%
South Korea (12, 7)	100%	28.6%	71.4%
Poland (42, 22)	85.7%	22.7%	63.0%
Russia (48, 21)	77.1%	4.8%	72.3%
Taiwan (31, 15)	93.5%	0%	93.5%
United States (65, 38)	83.1%	5.3%	77.8%
Overall	85.1%	6.9%	78.2%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 16: PASI 90 Response at Week 16 by Country for Trial 3001

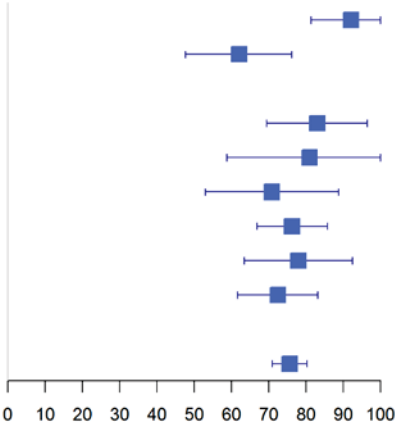
Subgroups (n[G], n[P])	Guselkumab (N=329)	Placebo (N=174)	Difference
Country			
Australia (23, 13)	69.6%	7.7%	61.9%
Canada (50, 24)	76.0%	0%	76.0%
Germany (41, 23)	51.2%	0%	51.2%
Spain (8, 4)	100%	0%	100%
Hungary (9, 7)	88.9%	0%	88.9%
South Korea (12, 7)	66.7%	0%	66.7%
Poland (42, 22)	85.7%	13.6%	82.1%
Russia (48, 21)	77.1%	0%	77.1%
Taiwan (31, 15)	74.2%	0%	74.2%
United States (65, 38)	70.8%	2.6%	68.1%
Overall	73.3%	2.9%	70.4%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 17: IGA Score of 0 or 1 at Week 16 by Country for Trial 3002

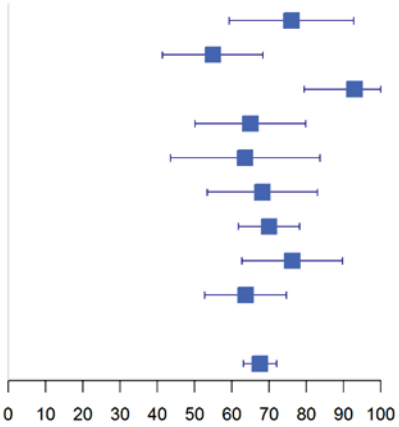
Subgroups (n[G], n[P])	Guselkumab (N=496)	Placebo (N=248)	Difference
Country			
Australia (25, 13)	92.0%	0%	92.0%
Canada (67, 30)	68.7%	6.7%	62.0%
Czech Republic (14, 9)	100%	0%	100%
Germany (40, 22)	87.5%	4.5%	83.0%
Spain (22, 10)	90.9%	10.0%	80.9%
South Korea (51, 23)	88.2%	17.4%	70.8%
Poland (133, 68)	88.0%	11.8%	76.2%
Russia (51, 24)	86.3%	8.3%	77.9%
United States (93, 49)	78.5%	6.1%	72.4%
Overall	84.1%	8.5%	75.6%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

Figure 18: PASI 90 Response at Week 16 by Country for Trial 3002

Subgroups (n[G], n[P])	Guselkumab (N=496)	Placebo (N=248)	Difference
Country			
Australia (25, 13)	76.0%	0%	76.0%
Canada (67, 30)	58.2%	3.3%	54.9%
Czech Republic (14, 9)	92.9%	0%	92.9%
Germany (40, 22)	65.0%	0%	65.0%
Spain (22, 10)	63.6%	0%	63.6%
South Korea (51, 23)	72.5%	4.3%	68.2%
Poland (133, 68)	71.4%	1.5%	70.0%
Russia (51, 24)	80.4%	4.2%	76.2%
United States (93, 49)	67.7%	4.1%	63.7%
Overall	70.0%	2.4%	67.5%



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population; Missing data imputed using NRI.

7.2.2. Additional Phase 3 Trial (Trial 3003)

7.2.2.1. Study Design and Endpoints

Trial 3003 was a randomized, double-blind, multicenter, Phase 3 trial comparing guselkumab and ustekinumab for the treatment of subjects with moderate-to-severe plaque-type psoriasis who had an incomplete response to ustekinumab (IGA ≥2) at Week 16. For enrollment subjects must have met the following key inclusion criteria:

- Male or female 18 years of age or older
- Diagnosis of plaque-type psoriasis for at least 6 months
- Candidates for either systemic therapy or phototherapy for psoriasis
- Have moderate-to-severe plaque psoriasis at screening and baseline defined by:
  - Investigator Global Assessment (IGA) score of at least 3 (moderate), see Figure 21in Appendix 13.3 for details on the IGA
  - Psoriasis Area and Severity Index (PASI) ≥12, see Figure 22 in Appendix 13.3 for details on the PASI
  - Body Surface Area (BSA) ≥10%

Subjects with non-plaque forms of psoriasis (e.g., erythrodermic, guttate, or pustular) or with drug-induced psoriasis (e.g., a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) were excluded. Subjects who had ever received guselkumab or ustekinumab were also excluded.

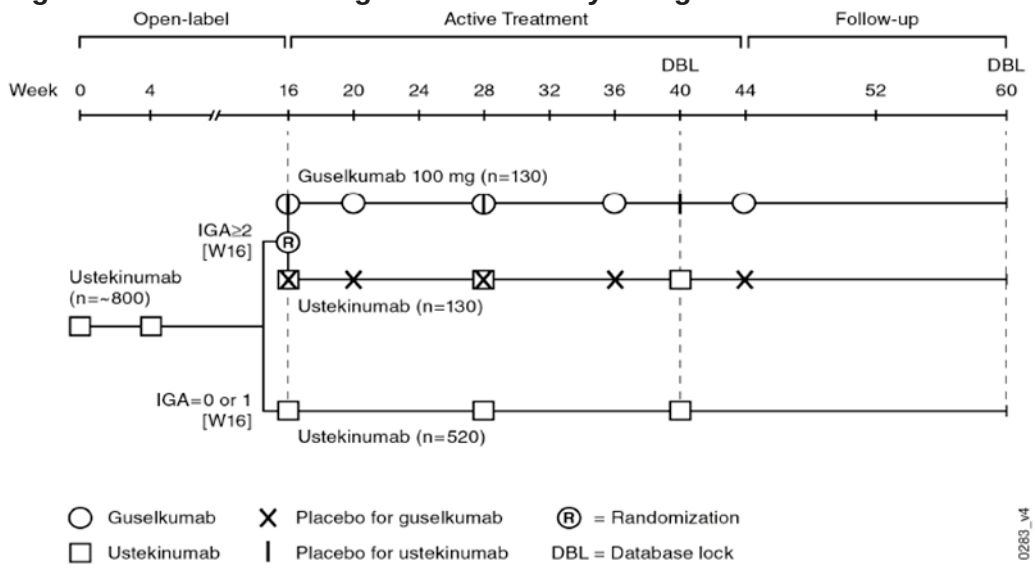
Figure 19 is the schematic diagram of the study design for Trial 3003. The trial was designed to enroll approximately 800 subjects from approximately 100 centers. All enrolled subjects were to receive open-label ustekinumab (STELARA®) at Weeks 0 and 4. At Week 16, subjects were assessed for efficacy according to the IGA, which determined their subsequent treatment:

- **Subjects with an IGA ≥ 2 at Week 16** were randomized in a 1:1 ratio to either switch to guselkumab or continue ustekinumab. Randomization was stratified by investigational site and baseline (Week 0) weight (≤100 kg, >100 kg). Subjects randomized to guselkumab received guselkumab 100 mg at Weeks 16, 20, 28, 36, and 44, and placebo for ustekinumab at Weeks 16, 28, and 40. Subjects randomized to ustekinumab continued to receive ustekinumab at Weeks 16, 28, and 40, and placebo for guselkumab at Weeks 16, 20, 28, 36, and 44.
- **Subjects with an IGA=0 or 1 at Week 16** continue to receive open-label ustekinumab at Weeks 16, 28, and 40.

The approved dosage for ustekinumab is based on weight. Subjects weighing ≤100 kg (220 lbs) received 45 mg, while subjects weighing >100 kg received 90 mg.

Subjects were evaluated at screening, baseline (Week 0), and Weeks 4, 16, 20, 24, 28, 32, 36, 40, 44, 52, and 60.

Figure 19: Schematic Diagram of the Study Design for Trial 3003



Source: protocol for Trial 3003

The primary efficacy endpoint specified in the protocol was the number of visits at which subjects achieve an IGA score of 0 or 1 and at least a 2-grade improvement (from Week 16) from Week 28 through Week 40 among randomized subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16. The visit interval (Week 28 to Week 40) includes a total of 4 visits; therefore, the possible number of visits for this endpoint ranges from 0 to 4.

The protocol/SAP specified the following as major secondary endpoints:

1. The number of visits at which subjects achieve a PASI 90 response from Week 28 through Week 40 among randomized subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16.
2. The number of visits at which subjects achieve an IGA score of 0 (cleared) from Week 28 through Week 40 among randomized subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16.
3. The proportion of subjects who achieve an IGA score of 0 or 1 and at least a 2-grade improvement (from Week 16) at Week 40 among randomized subjects with an inadequate (IGA≥2) response to ustekinumab at Week 16.

In regard to the primary and major secondary efficacy endpoints based on the number of visits, the Agency stated (advice letters dated October 15, 2014 and April 27, 2015) that using the number of visits as a combination of success and duration makes the interpretation of study findings difficult. In these advice letters, the Agency recommended comparing the response rates at a specific timepoint and comparing the duration of effect for those who achieve success.

The protocol for Trial 3003 specified many “other” secondary efficacy endpoints; however, these endpoints were not included in the multiplicity testing strategy. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

7.2.2.2. Statistical Methodologies

The protocol-specified primary analysis population was the randomized analysis set, defined as all randomized subjects. The SAP specified conducting supportive analyses using the per-protocol (PP) population, which was specified to include subjects who were compliant with the protocol. Specifically, the SAP defined the PP population to be all randomized subjects except those:

- Who did not satisfy the baseline inclusion and exclusion criteria
- Who had an IGA score of 0 or 1 at Week 16
- Who did not complete specified exposure to study product:
    - randomized to guselkumab group but did not receive all 4 assigned guselkumab injections at Week 16, Week 20, Week 28, and Week 36
    - randomized to ustekinumab group but did not receive all 2 assigned ustekinumab injections at Week 16 and Week 28
    - randomized to ustekinumab group but did not receive appropriate dose based on weight
    - received 1 or more incorrect active study agent prior to Week 40

For the analysis of the co-primary and major secondary efficacy endpoints, the protocol specified using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline weight (≤100 kg and >100 kg). The protocols specified using a sequential gatekeeping approach to control the Type I error rate for testing multiple secondary efficacy endpoints. The protocols specified testing the secondary efficacy endpoints in the order presented in Section 7.2.2.1.

Subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The applicant defined this as the “treatment failure criteria.” The SAP specified that baseline values will be assigned regardless of the observed data for continuous endpoints, zero will be assigned to improvement and percent change improvement, and non-responder status will be assigned to binary response variables.

After the treatment failure criteria is applied, the primary imputation method for the handling of missing data specified in the protocols for the primary and major secondary efficacy endpoints was the non-responder imputation (NRI) approach. The protocol specified the following as sensitivity analyses for the handling of missing data:

- Imputing missing data using LOCF
- Complete case analysis (i.e., missing data not imputed)
- Imputing missing data using the multiple imputation approach. The details regarding MI were not specified in the protocol or SAP. For the study report, the applicant imputed the missing data 5 times using a logistic regression model that included treatment group, baseline weight, and IGA score from Week 16 through Week 40 as factors.

7.2.2.3. Patient Disposition, Demographics and Baseline Disease Characteristics

A total of 871 subjects were enrolled and received open-label ustekinumab 45 mg or 90 mg (according to the subject’s baseline weight) at Weeks 0 and 4. At Week 16, all subjects were evaluated for efficacy according to the IGA. Of the 268 subjects with an IGA score ≥ 2 at Week 16, 135 subjects were randomized to receive guselkumab 100 mg at Weeks 16 and 20 then

Q8W thereafter, and 133 subjects were randomized to continue ustekinumab Q12W. The 585 subjects that had an IGA score ≤ 1 at Week 16 continued to receive open-label ustekinumab Q12W. Table 30 presents the disposition of subjects from Week 16 through Week 40. The discontinuation rate was higher in the ustekinumab arm compared to the guselkumab arm, which was primarily due to more subjects discontinuing due to lack of efficacy in the ustekinumab arm compared to the guselkumab arm.

Table 30: Disposition of Subjects From Week 16 Through Week 40

	Guselkumab (N=135)	Ustekinumab (N=133)
Discontinued	9 (7%)	16 (12%)
Adverse Events	3	2
Lack of Efficacy	3	9
Lost to Follow-up	0	1
Withdrawal by Subject	2	4

Source: Reviewer's Analysis (same as Applicant's Analysis); All subjects randomized at Week 16.

For both baseline (Week 0) and Week 16, the demographics and disease characteristics are presented in Table 31 and Table 32, respectively. For subjects randomized at Week 16, the demographics and disease characteristics were generally balanced across the treatment arms. It should be noted that the protocol specified obtaining affected BSA at only the screening and baseline (Week 0) visits.

Table 31: Demographics for Trial 3003

	Baseline	Week 16		
		Not Randomized[1]	Randomized[1]	
	Ustekinumab (N=871)	Ustekinumab (N=585)	Guselkumab (N=135)	Ustekinumab (N=133)
Age (years)				
Mean (SD)	43.1 (13.2)	42.9 (13.1)	44.2 (13.4)	43.0 (13.7)
Median	42	42	42	42
Range	18 – 84	18 – 84	19 – 74	20 – 78
18-64	818 (94%)	555 (95%)	122 (90%)	124 (93%)
≥ 65	53 (6%)	30 (5%)	13 (10%)	9 (7%)
Gender				
Male	566 (65%)	372 (64%)	95 (70%)	88 (66%)
Female	305 (35%)	213 (36%)	40 (30%)	45 (34%)
Race				
White	747 (86%)	523 (89%)	109 (81%)	99 (74%)
Black	13 (1%)	7 (1%)	3 (2%)	3 (2%)
Asian	103 (12%)	52 (9%)	22 (16%)	27 (20%)
Other	8 (1%)	3 (1%)	1 (1%)	4 (3%)
Weight (kg)				
Mean (SD)	88.3 (22.0)	86.8 (20.6)	90.3 (22.1)	91.3 (25.8)
Median	86.2	86.0	89.0	88.4
Range	43.2 – 188.6	46.0 – 177.0	43.2 – 180.5	44.0 – 188.6
≤ 100 kg	640 (73%)	436 (75%)	98 (73%)	96 (72%)
> 100 kg	231 (27%)	149 (25%)	37 (27%)	37 (28%)
Country				
US	194 (22%)	117 (20%)	42 (31%)	31 (23%)
Non-US	677 (78%)	468 (80%)	93 (69%)	102 (77%)

Source: Reviewer's Analysis (same as Applicant's Analysis)
(1) Subjects with an IGA score ≥ 2 were re-randomized to guselkumab or continue ustekinumab. Subjects with an IGA score ≤ 1 continued ustekinumab.

Table 32: Baseline Disease Characteristics for Trial 3003

	Baseline	Week 16		
		Not Randomized[1]	Randomized[1]	
	Ustekinumab (N=871)	Ustekinumab (N=585)	Guselkumab (N=135)	Ustekinumab (N=133)
IGA				
0 - Clear	0	203 (35%)	0	0
1 - Minimal	0	382 (65%)	0	0
2 - Mild	1 (<1%)	0	78 (58%)	83 (62%)
3 - Moderate	694 (80%)	0	55 (41%)	45 (34%)
4 - Severe	176 (20%)	0	2 (1%)	5 (4%)
PASI				
Mean (SD)	21.6 (9.2)	1.6 (1.9)	9.8 (7.7)	10.6 (8.1)
Median	18.6	1.2	7.6	9.1
Range	12 – 64.4	0 – 12.5	2 – 45	1 – 48
Percent BSA				
Mean (SD)	28.2 (16.8)	NA	NA	NA
Median	23	NA	NA	NA
Range	10 – 95	NA	NA	NA

Source: Reviewer's Analysis (same as Applicant's Analysis)
(1) Subjects with an IGA score ≥ 2 were re-randomized to guselkumab or continue ustekinumab. Subjects with an IGA score ≤ 1 continued ustekinumab.

7.2.2.4. Results for the Primary and Secondary Efficacy Endpoints

Table 33 presents the results for the primary and major secondary efficacy endpoint in the ITT population. For all of the primary and secondary efficacy endpoints, guselkumab was statistically superior to ustekinumab (p-values ≤ 0.001). The results (not shown) for the PP population were very similar to those presented in Table 33. In addition, the results (not shown) for the protocol-specified sensitivity analyses for the handling of missing data (i.e., LOCF, complete case, and multiple imputation) were similar to each other and to the primary imputation method (i.e., NRI).

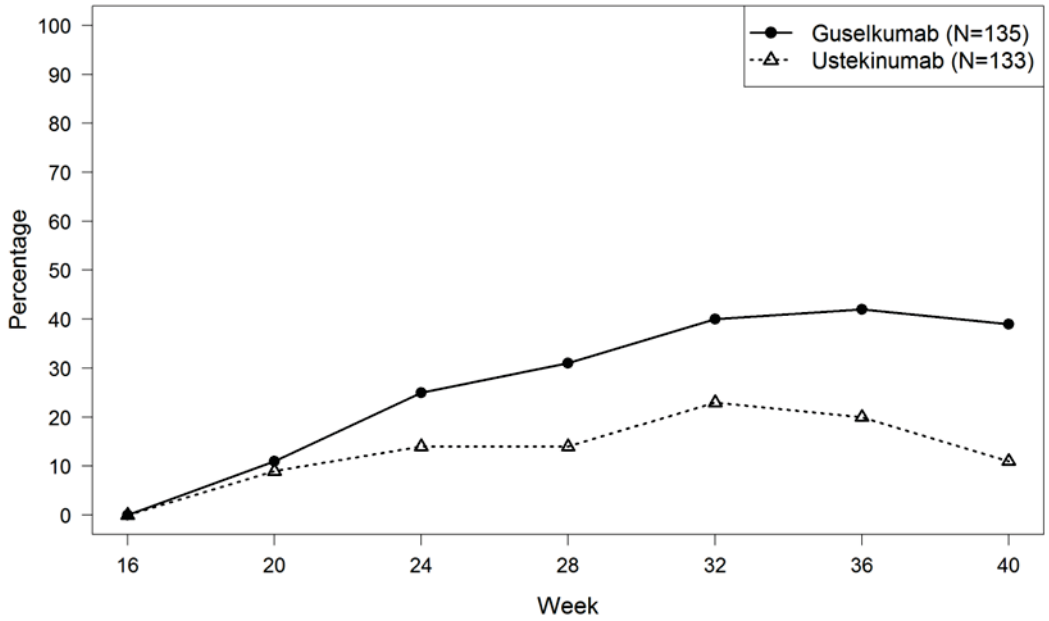
Figure 20 presents the results for IGA score of 0 or 1 with at least a 2-grade improvement (from Week 16) at Weeks 16 through Week 40.

Table 33: Results for the Primary and Major Secondary Efficacy Endpoints for Trial 3003

		Guselkumab (N=135)	Ustekinumab (N=133)	P-Value[(1)]
Primary Endpoint	**Number of visits (Week 28 through Week 40) at which subjects achieved an IGA score of 0 or 1 with ≥2-grade improvement (from Week 16)**			
	Mean (SD)	1.5 (1.6)	0.7 (1.3)	
	Median	1	0	
	Range	0 – 4	0 – 4	
	Categories (number of visits)			
	0	56 (41%)	96 (72%)	
	1	21 (16%)	11 (8%)	
	2	14 (10%)	7 (5%)	<0.001
	3	20 (15%)	10 (8%)	
	4	24 (18%)	9 (7%)	
Major Secondary Endpoints	**Number of visits (Week 28 through Week 40) at which subjects achieved PASI 90**			
	Mean (SD)	2.2 (1.7)	1.1 (1.5)	
	Median	3	0	
	Range	0 – 4	0 – 4	
	Categories (number of visits)			
	0	39 (29%)	76 (57%)	
	1	15 (11%)	19 (14%)	
	2	8 (6%)	7 (5%)	<0.001
	3	24 (18%)	10 (8%)	
	4	49 (36%)	21 (16%)	
	Number of visits (Week 28 through Week 40) at which subjects achieved an IGA score of 0			
	Mean (SD)	0.9 (1.3)	0.4 (1.1)	
	Median	0	0	
	Range	0 – 4	0 – 4	
	Categories (number of visits)			
	0	79 (59%)	115 (86%)	
	1	19 (14%)	3 (2%)	
	2	15 (11%)	4 (3%)	<0.001
	3	10 (7%)	4 (3%)	
	4	12 (9%)	7 (5%)	
	IGA score of 0 or 1 with ≥ 2-grade improvement (from Week 16) at Week 28	42 (31%)	19 (14%)	0.001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); All subjects randomized at Week 16; Missing data imputed using non-responder imputation (NRI).
(1) P-value based on a CMH test stratified by baseline weight (≤ 100 kg and > 100 kg).

Figure 20: IGA score of 0 or 1 with at least a 2-grade improvement (from Week 16) at Weeks 16 through Week 40



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); All subjects randomized at Week 16; Missing data imputed using non-responder imputation (NRI).

7.3. Review of Safety

7.3.1. Safety Review Approach

The primary review of safety of guselkumab for the treatment of moderate to severe plaque psoriasis focused on the evaluation of pooled data from 2 Trials 3001 and 3002. Both Phase 3 trials were similar with regard to design, study population, dosing regimen and key primary and secondary endpoints. The study designs which were identical up to Week 28 included a placebo comparator through Week 16 and active comparator up to Week 28. Subjects initially treated with placebo received guselkumab from Week 16 to Week 28. At Week 28, the designs were as follows:

- Trial 3001: subjects randomized to guselkumab and adalimumab continued the same treatment through Week 48 to allow assessment of the durability of response and comparative safety and efficacy with continuous exposure.

- Trial 3002: treatment for all subjects was based on their level of response at Week 28. Re-randomization of PASI 90 responders at Week 28 to guselkumab 100 mg or placebo provided data to compare the maintenance of response after withdrawal of guselkumab with continuous treatment. Refer to Section 7.2.1.1 for a description of the treatment groups after Week 28.

In the pooled safety database (Trials 3001 and 3002), a total of 1,367 subjects were treated with the proposed guselkumab dosing regimen of 100 mg, administered SC, at Weeks 0 and 4 and then q8w thereafter, including 592 subjects who were treated for 1 year.

The analysis of the pooled safety data from Trial 3001 and 3002) was conducted for the following 3 treatment periods:

1. Placebo-controlled Period: Week 0-16
   - Placebo
   - Guselkumab
   - Adalimumab

2. Common Active Comparator-Controlled Period: Week 0-28
   - Placebo (Week 0- 16)
   - Placebo → guselkumab: Safety data after crossover to guselkumab from placebo at Week 16
   - Guselkumab
   - Adalimumab

3. End of the Reporting Period: Week 0-48
   - Placebo: Subjects randomized to and treated with placebo (16 weeks) and safety data from the 12-week follow-up period for subjects who prematurely terminated the trial.
   - Guselkumab 100 mg: Safety data treated with guselkumab 100 mg includes:
     - Placebo → guselkumab 100 mg: Safety data after crossover to guselkumab 100 mg from placebo through Week 48.
     - Guselkumab 100 mg: Safety data from Week 0 through Week 48 for subjects

initially randomized to and treated with guselkumab.

- Adalimumab →Guselkumab 100 mg: Safety data after switch to guselkumab 100 mg from adalimumab through Week 48 in Trial CNTO1959PSO3002 (either at Week 28 for Week 28 nonresponders, or following loss of response after withdrawal from adalimumab for Week 28 responders)
- All Guselkumab: Safety data in all subjects treated with guselkumab 100 mg, that include:
  - Placebo →Guselkumab 100 mg: Safety data after crossover to guselkumab 100 mg from placebo through Week 48.
  - Guselkumab 100 mg: Safety data from Week 0 through Week 48 for subjects initially randomized to and treated with guselkumab.
  - Adalimumab → guselkumab 100 mg: Safety data after switch to guselkumab 100 mg from adalimumab through Week 48 (CNTO1959PSO3002).

- Adalimumab: Safety data for adalimumab subjects who are initially randomized to and received adalimumab only in Trial PSO3001 from Week 0 through Week 48 or in PSO3002 received treatment with adalimumab prior to receiving treatment with guselkumab or through Week 48 for those subjects who did not crossover to guselkumab.

The applicant did not demonstrate the bioequivalence of U.S. licensed and EU approved adalimumab. Therefore, data regarding the EU approved adalimumab was not included in the analysis. The sample sizes by treatment group are summarized below.

Table 34: Phase 3 Trial Treatment Groups

Trial	Treatment Group	# of subjects
3001	Placebo Week 0-16 (to guselkumab at Wk 16)	174
	Guselkumab	329
	Adalimumab (U.S. licensed)	115
3002	Placebo Week 0-16 (to guselkumab at Wk 16)	248
	Guselkumab	496
	Adalimumab (U.S. licensed)	81
3001/ 3002 Combined	Placebo Week 0-16 (to guselkumab at Wk 16)	422
	Guselkumab	823
	Adalimumab (U.S. licensed)	196
3003	Ustekinumab Wk 0,4	871
	Randomized to guselkumab at Wk 16	135
	Randomized to ustekinumab at Wk 16	133

Source: Reviewer's Table

The applicant submitted supportive safety data from the Phase 2 Trial PSO2001 and Phase 3 Trial 3003. This data was not pooled with safety data from Trial 3001 and 3002 because the Phase 2 trial had different dosing regimens and the Phase 3 trial had a different randomized study population (all subjects were exposed to ustekinumab). The applicant submitted other supportive safety data from 5 additional trials in other indications [palmoplantar pustulosis (PPP), rheumatoid arthritis (RA)] and other patient populations (Japanese subjects only)] and from the 120 Day safety update.

The review team analyzed following types of pooled data: exposure, demographics and baseline characteristics, prior psoriasis therapies, treatment emergent adverse events (TEAEs),

serious AEs (SAEs), and AEs leading to discontinuation. The applicant identified some adverse events of special interest (AESI) which included infections, malignancies, adjudicated cardiovascular (CV) events (including major adverse cardiovascular events [MACE]), and injection site reactions. The analysis of adjudicated MACE data included events from Trial PSO2001 and all 3 Phase 3 trials. In addition, the applicant submitted data from a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects enrolled in guselkumab clinical trials.

7.3.2. Review of the Safety Database

Overall Exposure

In two Phase 1 trials (1001 and 1002), a total of 76 adult subjects received a single dose of guselkumab. Of the 76 subjects, 36 were healthy volunteers and 40 were subjects with moderate to severe plaque psoriasis. Thirty of the healthy volunteers received a single intravenous (IV) dose of guselkumab ranging from 0.03 to 10 mg/kg; 6 received a single SC dose of 3 mg/kg. Of the 40 subjects with moderate to severe plaque psoriasis, 10 each received a single SC dose of 10, 30, 100, or 300 mg.

In the Phase 2 (Trial PSO2001) and Phase 3 (Trials 3001, 3002, and 3003) trials, a total of 1,748 subjects were treated with guselkumab. This number includes:

- Subjects who received treatment with guselkumab only
- Subjects who were crossed over from placebo to guselkumab in Trials PSO2001, 3001, and 3002
- Subjects who were crossed over from adalimumab to guselkumab in Trial 3002

Of the total 1,748 guselkumab-treated subjects in the Phase 2 and Phase 3 Trials, 1,393 were exposed for at least 6 months (24 weeks), and 728 were exposed for 1 year. Most of the subjects treated with guselkumab (1583/1748, 90.6%) received the proposed dose of 100 mg SC every 8 weeks. In Trial PSO2001, 41 subjects received doses of 200 mg SC. The average number of administrations was 5.0 across the Phase 2 and Phase 3 psoriasis trials.

Through the end of the reporting period in the pooled safety analysis set (Trials 3001 and 3002), a total of 1367 subjects received at least 1 injection of guselkumab. A total of 1036 subjects were treated for 6 months, and 592 subjects received treatment for 1 year. All subjects treated with guselkumab in Trials 3001 and 3002 received the proposed dose of 100 mg SC at Weeks 0 and 4, then every 8 weeks thereafter. This safety database is sufficient to evaluate the safety of guselkumab for the proposed indication in the target population.

In the 120 day safety update, the applicant reported an additional 1063 subject-years of follow-up after guselkumab exposure. Combined with 1022 subject-years of exposure during Week 0-48, this reveals a total exposure of 2085 subject-years of exposure to guselkumab. This includes subjects who crossed over to guselkumab after beginning treatment with adalimumab.

In addition, the applicant submitted safety information regarding exposure to guselkumab for subjects enrolled in five additional trials for other indications. A total of 304 subjects were exposed to guselkumab across these trials; 149 of these were healthy volunteers. Twenty-five subjects had palmoplantar pustulosis (PPP), and 21 subjects had generalized pustular

psoriasis/erythrodermic psoriasis (GPP/EP). A total of 109 subjects had rheumatoid arthritis (RA).

Relevant characteristics of the safety population:

Demographic characteristics of the subject population in the guselkumab development program are presented in greater detail in Section 7.2.1.3 of this review. A brief summary of demographic information relevant to the evaluation of safety will be presented here.

In Phase 3 Trials 3001 and 3002 (the pooled safety analysis set), the subjects were mostly White (82%) and male (70%). The median age was 43.5 years (range 18-87 years). The demographic characteristics were similar for the subjects enrolled in Phase 3 Trial 3003 and Phase 2 Trial PSO2001. Demographic characteristics were comparable across treatment groups in all 4 trials. Across these 4 trials, 93/1748 (5.3%) subjects treated with guselkumab were 65 years of age or older, of whom 4/1748 (0.2%) were at least 75 years of age.

In Trials 3001 and 3002, baseline disease characteristics were consistent with moderate to severe psoriasis and were similar across treatment groups. The median PASI score was 19.0, 76.1% had an IGA score of 3 and 23.8% had an IGA score of 4, and the median BSA involved was 23.0%. Among all randomized subjects in Trial 3003, the median PASI score was 19.3, the median BSA involved was 25.0%, 75.7% of subjects had an IGA=3, and 24.3% of subjects had an IGA=4. Among all randomized subjects in Trial PSO2001, the median PASI score was 18.2, the median BSA involvement was 20.0%, and 44.4% had a Physicians Global Assessment (PGA) of “marked” or “severe” (the PGA scale used in PSO2001 was different from the IGA scale used in Phase 3).

In Trials 3001 and 3002, the medical histories of the trial population were remarkable for significant cardiovascular risk factors:

- Hypertension in 25.7% and hyperlipidemia in 14.1%
- Diabetes mellitus in 8.8%
- Family history of early coronary artery disease (i.e. onset at <55 years of age) in 7.2%
- Tobacco exposure (i.e current or former smoker) in 51.3%

In Trials 3001 and 3002, less than 1% of subjects reported a history of squamous cell (SCC) or basal cell carcinoma (BCC) of the skin. A total of 17.9% of subjects in Trials 3001 and 3002 reported a history of cancer in a first degree family member other than skin SCC or BCC. Only 0.4% of the subjects in Trials 3001 and 3002 reported an infection that required hospitalization during the preceding year. Subjects in Trials 3003 and PSO2001 had similar medical histories to those of the subjects in Trials 3001 and 3002.

In Trials 3001 and 3002, 55.8% of subjects had received prior phototherapy and 63.3% had received prior nonbiologic systemic therapy. A total of 31.2% had received >1 such treatment previously. A total of 20.8% had received prior treatment with a biologic. A total of 30.1% of subjects in Trials 3001 and 3002 had never received prior treatment with systemic nonbiologic or biologic therapies. In Trial 3003, 53.7% of subjects had received previous phototherapy, 57.1% previously received nonbiologic systemic therapy, and 22.4% previously received biologic therapy. The histories of prior treatment were similar between treatment groups in Trials 3001, 3002, and 3003. In Trial PSO2001, 52.4% of subjects had received previous phototherapy, 52.4% previously received nonbiologic systemic therapy, and 40.9% previously

received biologic therapy. A total of 30.0% of subjects in Trial PSO2001 were naïve to nonbiologic systemic therapy or biologics.

Adequacy of the safety database:

The total subject exposure to guselkumab 100 mg SC at Weeks 0 and 4, followed by every 8 weeks for up to 48 weeks, provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of guselkumab for the treatment of moderate to severe plaque psoriasis.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of guselkumab. Data quality and fitness were evaluated in conjunction with the JumpStart team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

For the pooled safety analysis set, the applicant defined an adverse event (AE) as "any untoward medical occurrence in a clinical study subject administered a medicinal product". This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The adverse events included in analyses performed by the JumpStart team matched 100% to MedDRA dictionary version 18.1. The coding of adverse events in the BLA submission appeared adequate and allowed for accurate estimation of AE risks.

Investigators monitored each subject regularly for AEs or serious AE (SAEs) occurring throughout the trial. AEs and SAEs were recorded and reported from the time of signed and dated Informed Consent Form (ICF) was obtained until completion of the subject's last study-related procedure (which may have included contact for follow-up of safety).

Investigators categorized AE for seriousness, intensity, causality, duration, and action taken with study drug. All AEs or SAEs were followed until satisfactory resolution or a clinically stable or baseline status. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study drug, were to be reported using the Serious Adverse Event Form.

The applicant defined as treatment-emergent AEs (TEAE) those AEs that occurred after the start of initial study drug administration, as well as those AEs that were present at baseline but worsened in severity after the start of initial study drug administration. The applicant summarized TEAE for the pooled safety analysis set by treatment arm for each of the 3 analysis periods (Week 0-16, Week 0-28, and Week 0-48) for the following categories: any AEs, SAEs,

AEs leading to discontinuation of study drug, infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment.

A SAE, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, was defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important

If a serious and unexpected AE occurred for which there was evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event was to be reported as a serious and unexpected suspected AE.

The investigator made an assessment of intensity for each AE and SAE reported during the trial. The severity of each AE and SAE was recorded on the eCRF and was assigned to one of the following categories:

- **Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** Sufficient discomfort is present to cause interference with normal activity.
- **Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator made an assessment of the relationship between study product and the occurrence of each AE or SAE and categorized the potential relationship as follows:

- **Not Related:** An adverse event that is not related to the use of the drug.
- **Doubtful:** An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible:** An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- **Probable:** An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).
- **Very Likely:** An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant

disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

In addition to standard AE analyses, investigators analyzed AE by specific SOC and AE of special interest based on the following:

- mechanistic plausibility in the setting of immunomodulation via cytokine blockade (i.e., infections, malignancies)
- identified or potential safety concerns for other anti-cytokine antibody therapies (i.e, injection site reactions (ISRs), serious hypersensitivity reactions, and neuropsychiatric events)
- population risks previously identified within the target population with moderate to severe plaque psoriasis (i.e, adverse CV events [including MACE] and AEs of psoriasis)

For the rare and potentially serious AE of malignancies, CV events, and neuropsychiatric events (i.e, suicidal ideation and behavior) the applicant conducted additional analyses. The purpose of these analyses was to better understand the observed frequencies of events and to ensure that clinically relevant events were not missed. This included adjudication of potential CV events and potential events of suicidal ideation and behavior.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable. The applicant's identification and presentation of AE of special interest was appropriate.

Routine Clinical Tests

In Trials 3001 and 3002 (the pooled safety analysis set), the evaluation of safety was conducted during visits to the clinic. Scheduled visits occurred at Screening, Week 0, 2, and 4, followed by every 4 weeks through Week 48. The evaluation of safety included clinical laboratory tests, vital signs, physical examinations, ECGs, and evaluation for TB. These will be discussed in more detail below. Safety monitoring also included recording of adverse events, which was discussed in the previous section.

Clinical laboratory evaluation included hematology, serum chemistry, and lipid panel. In addition, serology for Hepatitis B and C, as well as a HIV antibody test were performed at Screening. Urine pregnancy testing was performed at every visit throughout the trial from Screening through Week 160.

Hematology [hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, lymphocytes, monocytes, neutrophils, bands, eosinophils, basophils, and platelet count] and serum chemistry [albumin, alkaline phosphatase, alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), total carbon dioxide (CO2), total bilirubin, urea, calcium, chloride, creatinine, glucose, potassium, total protein, sodium, high-sensitivity C-reactive protein, and follicle-stimulating hormone beta subunit (specific to women of non-childbearing age)] parameters were assessed at Screening, Week 0, then every 4 weeks until Week 24, then every 8 weeks from Week 24-48. A lipid panel [total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), total cholesterol to HDL ratio, and triglycerides] was assessed at Week 0.

Vital signs were assessed at every clinic visit during the trials. Measurement of vital signs included resting pulse rate and blood pressure. Height and weight were measured at Week 0; weight was also measured at Week 48. If any clinically significant changes in vital signs were noted, they were to be reported as AEs and followed to resolution or until a clinically stable endpoint was reached.

Physical examinations, including an examination of the skin, were performed at Screening and Week 48. Any new finding that was clinically significant in the opinion of the investigator was captured as an AE.

Supine 12-lead ECGs were performed at Week 0, 16 and 48 and read by an experienced reader at a central facility. Twelve-lead ECGs were recorded, and the data were stored in digital format. When scheduled on the same day as a blood sample collection or measurement of vital signs, the ECG was to be performed first. Any clinically significant abnormality in ECG parameters was recorded as an AE and was to be followed until a clinically stable endpoint had been reached.

Subjects were evaluated for signs and symptoms of active TB at scheduled visits or by telephone contact approximately every 8 to 12 weeks. Subjects were asked the following questions:

- **"**Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there was uncertainty as to whether a contact should be considered "close," a physician specializing in TB was to be consulted.)

If investigators suspected that a subject may have TB reactivation or new TB infection, they were to undertake an immediate and thorough investigation. This was to include, where possible, consultation with a physician specializing in TB. Subjects with evidence of active TB were to be referred for appropriate treatment.

Subjects who experienced close contact with an individual with active TB during the conduct of the study were to have a repeat chest radiograph and a repeat QuantiFERON® TB Gold test. In countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, a repeat tuberculin skin test was to be performed. Also, if possible, subjects were to be referred to a physician specializing in TB to determine the subject's risk of developing active TB and to determine the need for treatment for latent TB.

Study drug administration was to be interrupted during the investigation. A positive QuantiFERON® TB Gold test or tuberculin skin test result was to be considered detection of latent TB. If the QuantiFERON® TB Gold test result was indeterminate, the test was to be repeated as outlined in the protocol. Subjects who discontinued treatment for latent TB

prematurely or who were noncompliant with therapy were to immediately discontinue further administration of study drug and were encouraged to return for all subsequent scheduled study visits according to the Time and Events Schedule.

Supportive safety data was provided by Trial 3003. In Trial 3003, the evaluation of safety was conducted during visits to the clinic. Scheduled visits occurred at Screening, Week 0 and 4, then every 4 weeks from Week 16 to 44, followed by every 8 weeks through Week 60. The evaluation of safety included clinical laboratory tests, vital signs, physical examinations, ECGs, and assessment for TB. These will be discussed in more detail below. Safety monitoring also included recording of adverse events, which are discussed in previous subsection of this review.

Laboratory studies performed during Trial 3003 included the same tests as those performed during Trials 3001 and 3002. Hematology and blood chemistry parameters were measured at Screening and Week 0; a lipid panel was performed at Week 0. Hematology and blood chemistry studies were performed every 4 weeks from Week 16 to 24, then at Week 32, 40, 52, and 60. Urine pregnancy testing was performed regularly throughout the trial from Screening through Week 60.

Measurement of vital signs included resting pulse rate and blood pressure and was performed at every clinic visit during the trial. Physical examinations, including an examination of the skin, were performed at Screening and Week 60. As in Trials 3001 and 3002, any new finding that was clinically significant in the opinion of the investigator was captured as an AE. A supine 12-lead ECG was performed at Week 0 and read by a central facility. The assessment of subjects for TB reactivation or new infection in Trial 3003 was similar to that conducted in Trials 3001 and 3002.

7.3.4. Safety Results

Deaths

Five deaths were reported across the 6 primary trials in the development program until the initial database lock (2 subjects received guselkumab, 1 subject received adalimumab, 1 subject received ustekinumab and 1 subject received ustekinumab/guselkumab)

- 3001: 54 year old White male (#10993) with a history of morbid obesity, diabetes mellitus, methotrexate therapy for psoriasis who developed abdominal wall cellulitis on Day 33 after 2 doses of **adalimumab**. Subsequently, he developed ischemic hepatitis on Day 120 and later methicillin-resistant staphylococcus aureus (MRSA) pneumonia after a prolonged hospitalization. He died on Day 222. Assessed as not related.

- 3003: 59 year old White male (#30288) with a history of alcohol use was diagnosed with pancreatic cancer with liver metastasis after 2 doses of **ustekinumab** 45 mg (open label) and died within 1 month. Assessed as possibly related.

- PSO2001: 55 year old obese White male (# 0103-0206) with a history of smoking and alcohol use who developed hyperlipidemia while receiving **guselkumab** (5 mg q12w X 3 doses) and experienced a myocardial infarction on Day 194. He died in the ICU on Day 208 after progressive deterioration of his status. The association with guselkumab was assessed as possible. This case was reviewed by the cardiology consultant, Dr. Karen Hicks, who indicates that this event cannot be “definitively” attributed to guselkumab. (Review by Karen A. Hicks, M.D., dated 4/17/2017.)

Deaths Occurring After the Reporting Period (Week 48)

- 3001: 43 year old White male (#10990) with a history of treatment with citalopram for depression, discontinued the antidepressant during the trial. He reported an exacerbation of depression (Day 438), restarted citalopram but subsequently died (Day 492) as a result of suicide, following 10 doses of **guselkumab**. The event of suicide was assessed as not related. This case was reviewed by John C. Umhau MD, Medical Officer from the Division of Psychiatry Products (DPP) who stated that this event is not likely to be related to guselkumab based on "the classical understanding of cytokine effects on mood and impulsivity." (Refer to the review by John C. Umhau MD, dated 4/10/2017.)

- 3003: 67 year old White male (#30102) with a history of alcohol use and treatment with methotrexate for psoriasis, reported a 6 -week history of a left neck mass with palpable lymph nodes. He was diagnosed at Week 60 (Day 417), with a squamous cell carcinoma originating in the nasopharynx following 5 doses of **guselkumab** (last dose at Week 44) and 2 doses of **ustekinumab**. He received chemotherapy and died 9 months after diagnosis. Assessed as possibly related.

Serious Adverse Events

In the pooled safety analysis set (3001 and 3002), serious adverse events (SAEs) were analyzed by treatment period (Week 0-16, Week 0-28 and Week 0- 48). This analysis does not include data from subjects treated with EU approved adalimumab.

Placebo controlled period (Week 0-16)
In the **pooled safety analysis** set from **Week 0-16**, the proportion of subjects who experienced a SAE was 6.3 per 100 subject-years of follow-up in the guselkumab group (16/823, 1.9%), 4.7 per 100 subject-years of follow-up (6/422, 1.4%) in the placebo group, and 8.2 per 100 subject-years of follow-up (5/196, 2.6%) in the US licensed adalimumab group.

In the guselkumab group, all SAEs were single events except for non-cardiac chest pain which was reported by 2 subjects (2/823=0.2%). There were no clear trends that were included in labeling.

System Organ Classes (SOCs) in which multiple guselkumab treated subjects reported SAEs were the following:

- Cardiac disorders SOC: 3 subjects (0.4%) in the guselkumab group, 1 (0.5%) subject in the adalimumab (U.S. licensed) group and 0 subjects in the placebo group
- Musculoskeletal and connective tissue disorders SOC: 2 subjects (0.2%) in the guselkumab group, 0 subjects in the adalimumab (U.S. licensed) group and 2 (0.5%) subjects in the placebo group.
- General disorders and administration site conditions SOC: 2 subjects (0.2%) in the guselkumab group, no subjects in the adalimumab (U.S. licensed) group and no subjects in the placebo group
- Nervous system disorders SOC: 2 subjects (0.2%) in the guselkumab group, 0 subjects in the adalimumab (U.S. licensed) group and 0 subjects in the placebo group
- Renal and urinary disorders SOC: 2 subjects (0.2%) in the guselkumab group, 0 subjects in the adalimumab (U.S. licensed) group and 0 subjects in the placebo group

Table 35: Serious Adverse Events by Treatment Group: Guselkumab, Placebo and U.S. licensed Adalimumab

Body System Organ Class	Dictionary Derived Term	Treatment Group		
		Guselkumab	Placebo	Adalimumab
Cardiac disorders	Angina unstable	1 (0.12%)	0 (0.00%)	0 (0.00%)
	CAD	1 (0.12%)	0 (0.00%)	0 (0.00%)
	MI	1 (0.12%)	0 (0.00%)	1 (0.51%)
GI disorders	GI hemorrhage	0 (0.00%)	1 (0.24%)	0 (0.00%)
General disorders and admin site conditions	Non-cardiac chest pain	2 (0.24%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders	Cholecystitis	1 (0.12%)	0 (0.00%)	0 (0.00%)
	Cholecystitis chronic	0 (0.00%)	1 (0.24%)	0 (0.00%)
Infections & infestations	Cellulitis	0 (0.00%)	0 (0.00%)	2 (1.02%)
	Erysipelas	1 (0.12%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications	Cervical vertebral fracture	0 (0.00%)	0 (0.00%)	1 (0.51%)
	Clavicle fracture	1 (0.12%)	0 (0.00%)	0 (0.00%)
Investigations	ALT increased	1 (0.12%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tiss disorders	Intervertebral disc protrusion	1 (0.12%)	0 (0.00%)	0 (0.00%)
	Musculoskel pain	0 (0.00%)	1 (0.24%)	0 (0.00%)
	Osteoarthritis	0 (0.00%)	1 (0.24%)	0 (0.00%)
	Spondylolisthesis	1 (0.12%)	0 (0.00%)	0 (0.00%)
Nervous system disorders	Myelitis transverse	1 (0.12%)	0 (0.00%)	0 (0.00%)
	Paresthesia	1 (0.12%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders	Anxiety	0 (0.00%)	1 (0.24%)	0 (0.00%)
	Psychotic disorder	1 (0.12%)	0 (0.00%)	0 (0.00%)
	Suicide attempt	0 (0.00%)	0 (0.00%)	1 (0.51%)
Renal & urinary disorders	Calculus ureteric	1 (0.12%)	0 (0.00%)	0 (0.00%)
	Renal colic	1 (0.12%)	0 (0.00%)	0 (0.00%)
Skin & subcu tiss disorders	Psoriasis	0 (0.00%)	1 (0.24%)	0 (0.00%)
Vascular disorders	Periph art stenosis	0 (0.00%)	0 (0.00%)	1 (0.51%)
	Subjects	16 (1.94%)	6 (1.42%)	5 (2.55%)
	Subjects(total)	823 (100%)	422 (100%)	196 (100%)

Source: Reviewer's Table, JReview (Adalimumab= U.S. licensed only)
Myocardial infarction =MI
Alanine aminotransferase=ALT
Coronary artery disease=CAD
Peripheral artery stenosis= Periph art stenosis
Tissue=tiss

Common Active Comparator-Controlled Period (through Week 28)
In the pooled safety analysis set from **Week 0-28**, the proportion of subjects who experienced a SAE was slightly higher in the guselkumab group (28/823, 3.4%) than in the placebo (13/422, 3.1%) and US licensed adalimumab (5/196, 2.6%) groups.

A total of 47 SAEs occurred through Week 28 in subjects receiving guselkumab, U.S. licensed adalimumab, and placebo. In the guselkumab group, all SAEs were single events, except for non-cardiac chest pain and myocardial infarction [reported by 2 subjects each (0.2%)]. System

Organ Classes (SOCs) in which ≥3 guselkumab treated subjects reported SAEs were the following:

- Cardiac disorders; 6 subjects (0.7%) in the guselkumab group, 1 (0.5%) subjects in the adalimumab (U.S. licensed) group and 1 subject (0.3%) in the placebo /guselkumab group reported SAEs. Cardiac disorders reported by subjects exposed to guselkumab included: myocardial infarction (2 subjects), myocardial ischemia, cardiac failure, angina unstable, coronary artery disease and sinus node dysfunction.

- Infections and infestations: 3 subjects (0.4%) in the guselkumab group, 2 (1.0%) subjects in the adalimumab (U.S. licensed) group and 2 subjects (0.5%) in the placebo /guselkumab group reported SAEs. Infections among subjects exposed to guselkumab included: anal abscess, bronchitis, erysipelas, soft tissue infection and wound infection.

- Renal and urinary disorders SOC: 3 subjects (0.4%) in the guselkumab group, 0 subjects in the adalimumab (U.S. licensed) group and 0 subjects in the placebo group. Renal disorders among subjects exposed to guselkumab included: acute kidney injury, calculus ureteric and renal colic.

Through the End of the Reporting Period (Week 48)
The incidence of SAEs was comparable between the groups receiving continuous guselkumab or continuous adalimumab (U.S. licensed) from Week 0-48 [guselkumab: 30 (4.7%) and adalimumab (U.S. licensed): 5(4.3%)].

Over the entire treatment period (Week 0 to 48), serious adverse events were reported in 3.9% of subjects treated with guselkumab (5.6 per 100 subject-years of follow-up), and in 1.4% of subjects treated with placebo (4.7 per 100 subject-years of follow-up) and in 3.6% of subjects treated with U.S. licensed adalimumab (4.9 per 100 subject-years of follow-up).

Consistent with shorter reporting periods, the highest exposure-adjusted rates for SAEs among subjects treated with guselkumab were in the infections and infestations SOC and the Cardiac disorders SOC. There were no reports of SAEs related to opportunistic infections including tuberculosis in subjects exposed to guselkumab.

Table 36: Serious Adverse Events through Week 48 by MedDRA System Organ Class (3001 and 3002)

MedDRA System Organ Class (SOC)	Treatment Group				
	Continuous Guselkumab	Continuous Adalimumab	Guselkumab	Adalimumab U.S. licensed	Placebo
Subjects treated	641	115	1221	196	422
Av Duration of FU (Weeks)	46.1	44.9	0 (0.00%)	37.8	15.9
Av # injections	25.7	29.1	0 (0.00%)	23.7	10.6
# Subj with SAE	30 (4.7%)	5 (4.3%)	48 (3.9%)	7 (3.6%)	6 (1.4%)
SOC					
Infections &infest	7 (1.1%)	3 (2.6%)	10 (0.8%)	3 (1.5%)	0 (0.0%)
Cardiac disorders	3 (0.5%)	0 (0.0%)	7 (0.6%)	1 (0.5%)	0 (0.0%)
Injury, poisoning & procedural complic	2 (0.3%)	1 (0.9%)	6 (0.5%)	1 (0.5%)	0 (0.0%)
Musculoskeletal & connetv tiss disorders	1 (0.2%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	2 (0.5%)
GI disorders	4 (0.6%)	0 (0.0%)	5 (0.4%)	0 (0.0%)	1 (0.2%)
Nervous system disorders	2 (0.3%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	1 (0.2%)	0 (0.0%)	1 (0.1%)	1 (0.5%)	1 (0.2%)
Skin & subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.2%)
Blood and lymphatic system disorders	1 (0.2%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Congenital, familial and genetic disorders	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
General disorders and admin site conditions	2 (0.3%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorder	2 (0.3%)	2 (1.7%)	2 (0.2%)	2 (1.0%)	1 (0.2%)
Immune disorders	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Neoplasms	1 (0.2%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Renal & urinary disorders	3 (0.5%)	0 (0.0%)	4 (0.3%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular disorders	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.5%)	0 (0.0%)

*U.S. licensed
Source: Modified from Applicant's Table

The following are narratives of selected subjects who experienced SAEs during treatment with guselkumab.

- A 35 year old White male subject (#10233) with a history of depression, diabetes mellitus and psoriatic arthritis complained of bilateral plantar pain and foot weakness that had been ongoing for many years without much change. When the subject sought a definitive diagnosis, the neurologist determined that his symptoms were consistent with multiple

sclerosis (MS) and the subject discontinued the study treatment (Day 65). This SAE of MS is unrelated.

- A 37 year old White male subject (#10288) with a history of alcohol use and irritable bowel syndrome was hospitalized (Day 327) due to abdominal pain and vomiting. Endoscopy showed gastritis which was treated with pantoprazole and tramadol. The subject recovered from the SAE of gastritis. Although a relationship with the study product is unlikely, there is insufficient information regarding a potential infectious etiology such as helicobacter pylori or a virus to exclude a relationship entirely.

- A 25 year old White male subject (#10352) with a history of smoking experienced cellulitis (Study Day 288) and a postoperative wound infection (Day 314). After sustaining an injury in the gym one week earlier, the subject was hospitalized with leg pain arising from an inter-muscular hematoma of the right lower leg which was diagnosed by ultrasound. Surgeons performed an incision, irrigation, and drainage after the subject developed fever, marked hyperemia, and swelling of the right lower leg. Although he received treatment with ampicillin, gentamycin, and metronidazole, he experienced a postoperative wound infection after discharge from the hospital. He was readmitted and treated with amikacin and symptomatic therapy. The applicant assessed that the SAE of infection was unrelated. However, the role of immunosuppression associated with guselkumab exposure in the development of these infections cannot be excluded.

- A 57 year old White male subject (#10368) with a history of alcohol use, nephrolithiasis, and "heliotherapy" for psoriasis experienced multiple adverse events during the course of the trial including dysgeusia, mild leg discomfort and muscle spasm, a viral infection, injection site pain, prostatic dysplasia, urinary retention and a nodular basal cell carcinoma. Approximately 7 months after the initiation of the study product, the subject was informed that his prostate specific antigen (PSA) level rose from 3.7 to 4.7 (units not provided.) Trans-rectal ultrasound (TRUS) guided biopsy of the prostate indicated prostatic dysplasia (focal high grade prostatic intraepithelial neoplasia (PIN) in 1/10 biopsy samples. The applicant and investigator recommended that the subject discontinue the study product. Post-biopsy, the subject developed the SAE of urinary retention requiring catheterization (Day 282) which resolved and was assessed as not related to the study product. In addition, on Day 310 the subject was diagnosed with a nodular basal cell carcinoma (BCC) on the left-side of the nasal bridge. Per applicant, the SAE of urinary retention and PSA elevation were not related to the study product and BCC was possibly related. The subject had risk factors for cutaneous neoplasms including evidence of excessive sun exposure (e.g. actinic keratosis) noted at screening. However, the role of immunosuppression associated with guselkumab exposure in the development of malignancy cannot be excluded.

- A 44 year old Black female (#20516) with a history of migraine headache and alcohol use, experienced a headache, syncope and loss of consciousness on Day 179 and multiple seizures on Day 198 after 2 doses of guselkumab (last dose Day 146). CT scan without contrast and MRI were unremarkable and EEG was normal. Headache, syncope and seizures were assessed as doubtfully related. The subject completed the trial but received only placebo after the event. There was insufficient historical information to assess a relationship with guselkumab.

- A 28 year old White female (#20269) with no personal or family history of autoimmune disease who experienced multiple infections during her course of treatment with

guselkumab (URI, viral gastroenteritis, sinusitis treated with amoxicillin) developed thrombocytopenia on Day 169 after 4 doses of guselkumab. Her lowest platelet count was 27k U/L (NR: 130-400 kU/L). The subject withdrew from the trial due to this AE which resolved in approximately 2 months without the recommended hematology consultation. The relationship to guselkumab was assessed as doubtful (last dose was 5 weeks prior to onset of thrombocytopenia).

- A 35 year old White female (#20675) with a history of symmetrical numbness of the upper extremities, hypothyroidism, vitamin D deficiency, migraine, and rheumatoid arthritis and prior treatment with cyclosporine, infliximab and methotrexate was hospitalized with progressive numbness and weakness of her lower extremities on Day 35 after 2 doses of guselkumab. Multiple MRIs showed a lesion at cervical spine level 5, consistent with transverse myelitis and multisegmental osteochondrosis in the thoracic spine thought to be related to RA. Cerebrospinal fluid examination showed increased protein with no evidence of malignant cells. She was treated with diclofenac, pregabalin and corticosteroids with some improvement. The relationship to guselkumab was assessed as doubtful but the study product was withdrawn due to this AE. Although there is a temporal relationship to guselkumab administration, the event appeared to be part of an ongoing process which was not likely to be related.

- A 57 year old White male (#10859) with a history of gastroesophageal reflux disease, diabetes and hypertension experienced paresthesia of his left arm and pain of his left shoulder which radiated to his left chest after an argument with his son on Day 51 after 2 doses of guselkumab. Diagnostic test results (chest radiograph, electrocardiogram, echocardiogram, magnetic resonance imaging of the head, electrolytes, liver function, and ferritin bearing lymphocytes) were unremarkable. The event resolved spontaneously after 2-3 hours. The event of paresthesia was assessed as doubtful.

- A 32 year old White male (#10204) with a history of ongoing intense physical training and use of creatine powder and other dietary supplements to increase muscle mass experienced elevation of his liver enzymes and acute renal failure caused by rhabdomyolysis on Day 147 after 4 doses of guselkumab. Ultrasound revealed no urinary obstruction and the subject was treated with IV hydration. Acute kidney injury was assessed as not related and the subject completed the trial.

- A 24 year old White male (#10797) with a history of smoking and alcohol use and severe psoriasis since age 6 years with concomitant medications including methylprednisolone and prednisolone, was hospitalized with acute psychosis and schizophrenia on Day 74. The event was assessed as doubtfully related and guselkumab was withdrawn on ~Day 110 due to non-compliance. There is insufficient information regarding the dose and frequency or oral corticosteroid administration to allow assessment of the role of concomitant medications.

SAE in Trial 3003

Serious adverse events (SAEs) occurred in 5 (5/135, 3.7%) subjects randomized at Week 16 to treatment with guselkumab in Trial 3003. Determination of causality is somewhat confounded because all subjects were treated with ustekinumab at Week 0 and 4. Serious AE in subjects treated with guselkumab are described below:

- A 69 year old female (Subject 30107) with a past medical history (PMH) of HTN and hyperlipidemia had a myocardial infarction (MI) on Day 173. The subject had received 3 doses of guselkumab prior to the event; the most recent was Day 169. Investigators judged the AE severe, and not related to study treatment. Investigators reported the AE resolved by Day 181, and the subject continued treatment with guselkumab in the trial.

- A 52 year old male (Subject 30883) with a PMH of psoriatic arthritis and cigarette smoking (2 packs/day) sustained a MI on Day 122. The subject had received 1 dose of guselkumab prior to the event, on Day 113. Investigators classified the AE as severe, with possible relation to study treatment. The AE resolved on Day 124, and the subject continued treatment with guselkumab and completed the study.

  These cases were reviewed by the cardiology consultant, Dr. Karen Hicks, who noted that both subjects had risk factors for MI. Dr. Hicks' review concludes that "Based on the available data at this time, we do not observe evidence of clinically meaningful imbalance in MACE or "other CV events" with guselkumab". (Refer to the review by Karen A. Hicks, M.D., dated 4/17/2017.)

- A 69 year old female (Subject 30573) with a hematuria from Day 122-134 was diagnosed with transitional cell carcinoma of the bladder on Day 156. The subject had received 1 dose of guselkumab prior to the onset of hematuria and 2 doses of guselkumab prior to diagnosis of the transitional cell carcinoma; the most recent was Day 141. Investigators judged the AE to be of moderate severity, with relationship to study treatment "doubtful". The subject underwent resection of the tumor, and investigators termed the AE resolved on Day 161. The subject discontinued from study drug, but continued participation until completing the safety follow-up visit at Week 40.

- A 30 year old male (Subject 30698) had a partner with ectopic pregnancy on Day 209 of the trial. The subject had received 3 doses of guselkumab prior to the event; the most recent was Day 195. Investigators judged the AE to be of moderate severity, and not related to study treatment. The AE resolved with termination of the pregnancy on Day 277. The subject continued treatment with guselkumab and completed the trial.

- A 40 year old male (Subject 30800) with a PMH of bipolar affective disorder, chronic drug dependency, attention deficit hyperactive disorder, and personality disorder had an episode of acute multi-drug intoxication (cocaine, methadone, ethanol, opiates, and benzodiazepines) on Day 147. The subject had received 2 doses of guselkumab prior to the event; the most recent was Day 142. While hospitalized, the subject denied suicidal intent, but admitted to the use of the substances 1 to 2 days before hospitalization to overcome stress. Liver function studies were elevated at the time of initial evaluation for the intoxication, and had begun to improve the following day. Investigators judged the AE to be of moderate severity, and not related to study treatment. The AE was declared resolved on Day 148, and the subject was discontinued from the trial.

For the results of the analysis of the overall rate of SAEs by demographic subgroup refer to Appendix 13.3.

The applicant evaluated the risk of infection including serious infections and the risk of reactivation of tuberculosis during the clinical trials. In Trials 3001 and 3002, infections occurred in 23% of subjects in the guselkumab group versus 21% of subjects in the placebo group through 16 weeks of treatment. Upper respiratory tract infections, tinea infections and herpes

simplex infections occurred more frequently in the guselkumab group than in the placebo group. The rate of serious infections for the guselkumab group and the placebo group was ≤ 0.2%. Prior to the initiation of treatment, the applicant evaluated subjects for tuberculosis. In clinical studies, 105 subjects with latent tuberculosis (TB) who were concurrently treated with guselkumab and appropriate TB prophylaxis did not develop active TB (during the mean follow-up of 43 weeks). During and after treatment with guselkumab, monitoring is recommended for signs and symptoms of active TB.

Because of the risk of serious infection, live vaccines should be avoided and all age appropriate immunizations, according to current immunization guidelines, should be completed prior to the initiation of treatment with guselkumab.

The risk of serious infections, reactivation of tuberculosis and immunization with live vaccines will be communicated in product labeling (Section 5 WARNINGS AND PRECAUTIONS).

Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo controlled period through Week 16 in Trials 3001 and 3002, 11/823 (1.3%) subjects in the guselkumab group were discontinued because of an AE, compared to 0.9% in the placebo and 1% in the US licensed adalimumab groups.

In the guselkumab group, the SOC of Nervous System disorders had the highest number of discontinuations with 3/822 (0.4%). Two subjects In Trial 3001 and one subject in Trial 3002 in the guselkumab group were discontinued because of adverse events in the SOC of Nervous System Disorders:

- A 35 year old male (Subject 3001-10233) was discontinued because of an AE of multiple sclerosis. For further details, refer to “Serious Adverse Events” in this section of the review.

- A 21 year old female (Subject 3001-10774) was discontinued because of an AE of bilateral hand dysesthesia reported on Study Day 15. This event was assessed as mild in severity, was not serious, and resolved after study drug withdrawal.

- A 35 year old female (Subject 3002-20675) was discontinued because of an AE of transverse myelitis. For further details, refer to “Serious Adverse Events” in this section of the review.

One subject in Trial 3002 was discontinued because of drug-induced liver injury:

- A 48 year old male subject (Subject 3002-20839) in the guselkumab group of Trial 3002 was discontinued on Day 59 from study treatment due to an AE of drug-induced liver injury. The subject received guselkumab on Study Days 1 and 29. The investigator noted that this event was related to isoniazid therapy being administered for latent TB diagnosed pre-study and was not due to guselkumab therapy. The AE was not serious, moderate in severity, and was later resolved after discontinuation of isoniazid.

No subjects in the guselkumab group were discontinued because of an infection, and no individual AE led to discontinuation of guselkumab in >1 subject in any treatment group from Week 0-16.

During the Week 0-48 period through in Trials 3001 and 3002, 22/1221 (1.8%) subjects treated with guselkumab at any point were discontinued because of an AE, compared to 5/196 (2.6%) of subjects treated with US licensed adalimumab. In subjects treated with guselkumab at any point during the trial, the event rate for discontinuation because of AE decreased from 4.31/100 subj-yrs in Week 0-16 to 2.36 events/100 subj-yrs in Week 0-48. The SOC of Neoplasms had the highest number of discontinuations with 5/1221 (0.4%). These included 2 subjects with prostate cancer, 2 with squamous cell carcinoma, and 1 with invasive papillary breast carcinoma. These are discussed in more detail in Section 7.3.5 Analysis of Submission-Specific Safety Issues. One subject in the placebo → guselkumab group was discontinued because of an infection. The subject was a 36 year old with a history of asthma who was discontinued because of a nonserious AE of nasopharyngitis.

In the 120 day safety update, the applicant reported that a total of 5 subjects in Trials 3001 and 3002 who were treated with guselkumab discontinued treatment due to an adverse event after week 48 and prior to the cutoff date of 10/31/2016. In Trial 3001, there were 3 discontinuations: 1 in the guselkumab group (brain neoplasm) and 2 in the adalimumab → guselkumab group (pregnancy, worsening of psoriatic arthritis). In Trial 3002, there were 2 discontinuations. One was in the placebo → guselkumab-placebo group (during withdrawal) and was because of psoriatic arthritis. The other subject received continuous treatment with guselkumab and was discontinued due to prostate cancer. The cases of malignancy are discussed in more detail in Section 7.3.5 Analysis of Submission-Specific Safety Issues.

Significant Adverse Events

Refer to Section 7.3.5, “Analysis of Submission-specific Safety Issues”.

Treatment Emergent Adverse Events and Adverse Reactions

During the 16 week placebo-controlled period of Trials 3001 and 3002, treatment-emergent adverse events (TEAE) occurred in 49% of subjects in the guselkumab group, compared to 47% of subjects in the placebo group. The most common TEAE were in the system/organ class (SOC) of infections and infestations and included upper respiratory infections (URI), gastroenteritis, tinea infections, and herpes simplex infections. Data regarding TEAE for Trial 3003 are confounded because all subjects in this trial received ustekinumab prior to randomization at Week 16, and therefore will not be discussed here.

Because common AE were often reported under multiple preferred terms, we pooled these AE to better evaluate their overall frequency of occurrence (see Table 37 below). URIs, headaches, and injection site reactions were the most common TEAE and occurred in greater than 4% of subjects treated with guselkumab. Although these are common illnesses and symptoms, the difference in frequency of the TEAE between subjects treated with guselkumab and placebo was greater than 1%. Upper respiratory infections occurred most commonly, occurring in >10% frequency in all treatment groups. However, URI occurred more frequently in the guselkumab group (14.3%) than subjects in the placebo group (12.8%). None of the URI events were serious and none resulted in discontinuation of treatment.

Headache was the second-most commonly reported TEAE, occurring in 4.6% of subjects in the guselkumab group and 3.3% of the placebo group. Although the mean recorded duration was 33.2 days (range 1-282 days), the duration of headache was 3 days or fewer in 23/38 subjects. Vital signs in subjects with headache were normal in 33/38 subjects; abnormal vital signs included elevated blood pressure in 5/38 subjects. The reported severity of headache was mild

in 23/38 and moderate in 15/38 of subjects. Headaches resolved in 35/38, and were not resolved in 3/38 subjects. The relationship of headache to treatment was judged to be doubtfully or not related in 32/38, and possibly or probably related in 6/38 subjects. None of the headache events resulted in interruption or discontinuation of treatment.

Injection site reactions occurred in 4.5% of subjects in the guselkumab group. Approximately 95% of injection site reactions were of mild severity; the rest were of moderate severity. All injection site reactions resolved, and approximately two-thirds of injection site reactions resolved within 1 day. Investigators judged approximately 80% of injection site reactions to be possibly, probably, or very likely related to treatment with guselkumab. Injection site reactions did not correlate with the presence of anti-drug antibodies to guselkumab. No injection site reactions resulted in interruption of treatment.

Elevated liver enzymes occurred in 2.6% of subjects in the guselkumab group, compared with 2% in the placebo group. Elevated enzymes were mostly ALT and AST, and did not coincide with significantly elevated (>2x upper limit of normal range [ULN]) bilirubin levels. Most elevations were classified by investigators as mild or moderate in severity. Elevated liver enzymes were resolved or resolving in 85% of subjects and none resulted in interruption or discontinuation of treatment. One subject, a 25 year old female, had elevation of ALT at Week 8 which was categorized by investigator as severe. However, the maximum recorded ALT value was 90 which is greater than 3 times but less than 5 times the upper limit of normal. The applicant classified AE severity using CTCAE v 4.03; based on this classification scale the AE should have been classified as moderate in severity. The AE resolved and the subject continued in the trial.

Diarrhea occurred in 1.6% of subjects in the guselkumab group, compared to 0.9% in the placebo group. Although the mean duration of diarrhea was 18.2 days (range 1-96 days), the duration of diarrhea was 5 days or fewer in 10/13 of subjects. The reported severity of diarrhea was mild or moderate. The relationship of diarrhea to treatment was judged by investigators to be possibly related in 3/13, and doubtfully or not related in the remainder. Laboratory studies were normal in most subjects with AE of diarrhea; however 4/13 subjects had elevated ALT and AST. The maximum ALT levels were less than 3 times and maximum AST levels less than 2 times the upper limit of normal during the AE of diarrhea. However, these subjects experienced elevated ALT and AST levels at other timepoints during the study period which did not correlate temporally with an AE of diarrhea. Associated symptoms included nausea in 2/13, abdominal pain in 1/13, dyspepsia in 1/13, and headache in 1/13. Information regarding associated symptoms was not provided for 9/13 subjects. All of the diarrhea events resolved. None of the diarrhea events resulted in interruption or discontinuation of treatment.

Gastroenteritis was the second most common AE from the SOC of “Infections and Infestations”, and occurred in 1.3% of subjects in the guselkumab group, compared to 0.9% in the placebo group. Although the mean duration was 21.9 days (range 2-150 days), the duration of gastroenteritis was 6 days or fewer in 9/11 subjects. No information was provided regarding past medical history of inflammatory bowel disease, GERD, or irritable bowel syndrome in subjects with gastroenteritis. The reported severity of gastroenteritis was mild in 7/11 and moderate in 4/11 subjects. The relationship of gastroenteritis to treatment was judged to be possibly related in 2/11 and doubtfully related or not related in the remainder. Laboratory studies were normal in 10/11 subjects; 1/11 subjects had elevated ALT. However, this subject’s ALT level was elevated throughout the study period and did not correlate temporally with the AE of gastroenteritis. A reported associated symptom of upper abdominal pain was reported by

1/11 subjects; no information regarding associated symptoms was provided for the remainder. Additionally, the presence or absence of fever was not recorded for any subject with gastroenteritis. All of the gastroenteritis events resolved. None of the gastroenteritis events resulted in interruption or discontinuation of treatment.

Tinea infections occurred in 1.2% of subjects in the guselkumab group, compared to none in the placebo group. Although the mean recorded duration of tinea infection was 23 days (range 8-58 days), only 5/10 subjects had sufficient recorded data to determine duration (i.e. the study day of start and/or end of tinea infection was not recorded). The reported severity of tinea infection was mild in 7/10 and moderate in 3/10 (all with T. cruris) of subjects. The relationship of tinea infection to treatment was judged to be possibly related in 3/10, and not related in 7/10. All of the tinea infection events resolved. None of the tinea infection events resulted in interruption or discontinuation of treatment.

Herpes simplex infections occurred in 1.1% of subjects in the guselkumab group, compared to 0.5% in the placebo group. The mean duration was 9 days (range 5-24 days). The reported severity of HSV infection was mild in 8/9 and moderate in 1/9 of subjects. The relationship of HSV infection to treatment was judged to be possibly related in 5/9 (55.6%), and doubtfully or not related or in the remainder. All of the HSV infection events resolved. None of the HSV infection events resulted in interruption or discontinuation of treatment.

We compared the frequency of TEAE discussed above between the Week 0-16 and Week 0-48 time periods using number of AE/100 subject-years. URIs increased slightly from 52.5 events/100 subject-years from Week 0-16 to 55.3 events/100 subject-years from Week 0-48. The remaining AE showed a decrease in the number of events/100 subject-years between Week 0-16 and Week 0-48.

For the Adverse Reactions (section 6) section of product labeling, the applicant proposed to include (b) (4)

However, based on our review of the safety database, our conclusions revealed more adverse events occurring in greater than 1% of subjects treated with guselkumab and more frequently than in the placebo group. Table 37 displays TEAE occurring in >1% of subjects and more frequently than in the placebo group in Trials 3001 and 3002, along with the terms pooled for each AE, where applicable. These represent adverse reactions to be included in section 6 of product labeling.

Table 37: Adverse Reactions Occurring in ≥ 1% of Subjects through Week 16 in Trials 3001 and 3002

	Guselkumab * (N=823) n (%)	Adalimumab [a] (N=196) n (%)	Placebo (n=422) n (%)
Upper respiratory Infections[b]	118 (14.3)	21 (10.7)	54 (12.8)
Headache[d]	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions[c]	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Elevated liver enzymes [e]	21 (2.6)	4 (2.0)	8 (1.9)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis[f]	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections[g]	9 (1.1)	0	0
Herpes Simplex infections[h]	9 (1.1)	0	2 (0.5)

Source: Reviewer's Table, JReview
[a] U.S. licensed adalimumab
[b] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI
[c] Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.
[d] Headache includes headache and tension headache.
[e] Elevated liver enzymes includes increased alanine aminotransferase , increased aspartate aminotransferase , increased hepatic enzyme, increased transaminases, abnormal liver function test, and hypertransaminasemia.
[f] Gastroenteritis includes gastroenteritis and viral gastroenteritis (both from SOC of Infections and Infestations).
[g] Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.
[h] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.
* subjects receiving 100 mg of TRADENAME at Week 0, Week 4, and every 8 weeks thereafter

Laboratory Findings

Evaluation of systemic safety included assessment of clinical laboratory data in all of the core psoriasis trials. Investigators performed clinical laboratory testing during Phase 3 Trials 3001 and 3002 according to the schedule discussed in section 7.3.3 of this review. The effect of guselkumab on hematology and clinical chemistry parameters during each of the three analysis periods are discussed below.

<u>Week 0-16</u>

For each hematology parameter, 1.5% or fewer subjects in the guselkumab group had a value consistent with CTCAE grade ≥2 Week 0-16. No subject in the guselkumab group had a hematology value consistent with CTCAE grade 4, and only 2 subjects (0.2%) had a hematology value consistent with CTCAE grade 3 (both of decreased lymphocytes). The frequency of hematology laboratory values consistent with CTC

AE grade 2 or higher was similar in the placebo group.

Shift tables for hematology laboratory values showed that ≤3.5% of subjects in the guselkumab group had a shift from a normal baseline to a value below or above the laboratory normal range for hemoglobin, hematocrit, neutrophils, platelets, RBCs, WBCs, or lymphocytes. For each hematology parameter, the proportion of subjects in the guselkumab group with a shift from a normal baseline to a value outside the normal range at Week 16 was similar to or lower than that of the placebo or pooled adalimumab groups.

From Week 0 through 16, few (1.5% or fewer) subjects in the guselkumab group had an abnormal value consistent with CTCAE grade ≥2 for the following clinical chemistry parameters: albumin (decreased), creatinine (increased), ALT (increased), AST (increased), alkaline phosphatase (increased), total bilirubin (increased), sodium (increased or decreased), potassium (increased or decreased), calcium (increased or decreased), nonfasting glucose (decreased). The frequencies of chemistry laboratory values consistent with CTCAE grade 2 or higher in the guselkumab group were similar with those for the placebo group. No subject in any treatment group had a chemistry laboratory value consistent with CTCAE grade 4. The only chemistry abnormalities consistent with CTCAE grade 3 reported in more than 1 subject in the guselkumab group were elevated sodium (reported in 5 subjects) and elevated ALT (reported in 2 subjects).

Shift tables for chemistry laboratory values from Week 0-16 showed that <2% of subjects in the guselkumab group had a clinically relevant shift from a normal baseline to a value below or above the laboratory normal range for most of the clinical chemistry parameters evaluated. For each clinical chemistry parameter, the proportion of subjects in the guselkumab group with shifts from a normal baseline to an abnormal result at Week 16 was similar to or lower than that in the placebo or adalimumab groups. 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.

From Week 0-16, elevated liver enzymes (transaminases) were reported as an AE in 2.6% of subjects treated with guselkumab, 2.0 % of subjects treated with U.S. licensed adalimumab, and 1.9% of subjects treated with placebo. Elevated liver enzymes are discussed in more detail in Section 7.3.1.4 of this review and will be included in the Adverse Reactions section of product labeling.

<u>Week 0-28</u>

Hematology results for Week 0-28 were similar to those from Week 0-16; <2.0% of subjects in the guselkumab group had a hematology laboratory value consistent with CTCAE grade of ≥2 through Week 28. For most of these abnormalities, the maximum CTCAE grade was 2. There were 2 reports of CTCAE grade 3 hematology abnormalities in the guselkumab group (1 report each of decreased platelets and decreased neutrophils). No subject in the guselkumab group had a hematology laboratory value consistent with CTCAE grade 4. For each hematology parameter, the proportion of subjects in the guselkumab group with a laboratory value consistent with CTCAE grade ≥2 was similar to or lower than that of the adalimumab group. Among subjects who crossed over from placebo to guselkumab, the frequency of CTCAE grade ≥2 abnormalities in laboratory values was 1% or less for each hematology parameter. Most abnormal hematology laboratory results reported were sporadic and eventually improved without alteration or interruption of treatment.

Investigators reported one subject with an abnormal chemistry lab value consistent with CTCAE grade 4 from Week 0-28. The abnormality was elevated AST, and occurred in a 34 year old male subject treated with guselkumab in Trial 3001. The CTCAE grade 4 elevation in AST (795 U/L) occurred on Day 169; the subject's ALT value was also elevated (562 U/L, grade 3). The baseline value on Day 1 was normal at 28 U/L. The subject's ALT and AST values had been within the normal range or slightly elevated (grade 1) through Day 141, and values began to return toward baseline beginning on Day 171. Values for alkaline phosphatase and total bilirubin were not similarly elevated (Grade 0 or 1). There were no concomitant medications, conditions, or adverse events coinciding with the elevated transaminases. No past medical history was provided for this subject. The subject remained in the study and continued to receive treatment. The transaminase elevations were reported as an AE (hepatic enzymes increased), but were not considered serious. Laboratory values for ALT and AST continued to return toward baseline values and on Day 337 were 57 U/L (grade 1) and 33 U/L (normal), respectively.

Overall, few (2.5% or fewer) subjects in the guselkumab group had a clinical chemistry laboratory abnormality consistent with CTCAE grade 2 or higher. For most of these abnormalities, the maximum CTCAE grade was 2. For each clinical chemistry parameter, the proportion of subjects in the guselkumab group with CTCAE grade ≥2 abnormalities was similar to that of the adalimumab group. The most common chemistry abnormalities consistent with CTCAE grade ≥2 clinical 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. Among subjects crossed over from placebo to guselkumab, the frequency of laboratory values consistent with CTCAE grade ≥2 was 1.5% or less for each clinical chemistry parameter.

Week 0-48

Fewer than 3% of subjects in the guselkumab group had a hematology laboratory value consistent with CTCAE grade ≥2. For most of these abnormalities, the maximum CTCAE grade was 2, consistent with observations through Week 16 and Week 28. No subject in the guselkumab group had a hematology laboratory value consistent with CTCAE grade 4 from Week 0-48. There were no additional reports of CTCAE grade 3 hematology abnormalities in the guselkumab group.

The most common CTCAE grade ≥2 hematology abnormality in the guselkumab group was low lymphocyte counts, which occurred in 2.5% of subjects (n=31; maximum grade of 2 in 29 subjects and maximum grade of 3 in 2 subjects). For each hematology parameter, the proportion of subjects in the guselkumab group with a laboratory value consistent with CTCAE grade ≥2 was similar to or lower than that of the adalimumab group. Among subjects who crossed over from adalimumab to guselkumab, the frequency of laboratory values consistent with CTCAE grade ≥2 was ≤2% for each hematology parameter.

From Week 0-48, fewer than 3% subjects in the guselkumab group had a clinical chemistry laboratory value consistent with CTCAE grade of ≥2. For most of these abnormalities, the maximum CTCAE grade was 2, which is consistent with the observations for the Week 0-16 and Week 0-28 analysis periods. For each clinical chemistry parameter, the proportion of subjects with a laboratory value consistent with CTCAE grade ≥2 from Week 0-48 in the guselkumab group was similar to that of the adalimumab group. Similar to the Week 0-28 analysis period, the most common grade ≥2 clinical chemistry abnormalities from Week 0-48 were elevations of ALT, AST, and total bilirubin. Elevations of ALT, AST, and total bilirubin occurred in 2.8%,

2.7%, and 1.6%, respectively, of subjects in the guselkumab group and 4.2%, 1.9%, and 2.1%, respectively, of subjects in the adalimumab group.

ALT and AST elevations were also the most common CTCAE grade 3 abnormalities from Week 0-48, reported in 0.8% and 0.7%, respectively, in the guselkumab group and 0.7% and 0.9% in the adalimumab group. Among subjects crossed over from adalimumab to guselkumab, the frequency of CTCAE grade ≥2 laboratory values was <1% for each clinical chemistry parameter. Most abnormal clinical chemistry laboratory results reported from Week 0-48 were sporadic and eventually improved without alteration or interruption of treatment.

One additional subject had clinical chemistry abnormalities consistent with CTCAE grade 4 during the Week 0-48 period. This abnormality occurred in a subject under treatment with guselkumab in Trial 3001. This subject was a 28 year old female (Subject 10180) who experienced elevations in serum creatinine (1114 µmol/L) and potassium (7.3 µmol/L) consistent with CTCAE grade 4 on Study Day 344 (last laboratory evaluation before database lock). Blood urea nitrogen (BUN) was also elevated at 40.7 mmol/L. There were no other reported concomitant conditions, medications or adverse events coinciding with these laboratory abnormalities. No past medical history was provided for this subject. All preceding values for these laboratory parameters were within the normal range. The subject was not discontinued from treatment, and the laboratory abnormalities were not considered SAEs. The subject continued to receive study treatment. Data available after the database lock for this submission indicated that abnormal laboratory values for creatinine and potassium resolved spontaneously.

The evaluation of clinical laboratory data provided supportive safety information for Phase 1 Trials 1001 and 1002, Phase 2 Trial PSO2001, and Phase 3 Trial 3003.

In Trial 1001, there were no notable mean changes or dose-related trends in laboratory measurements among the 20 subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg.

For the most part, in Trial 1002 there were no trends or dose-related changes in clinical laboratory evaluations observed among the 20 Japanese subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg. However, 2 subjects (1 each in the 100 and 300 mg group) experienced a marked but transient increase in creatine kinase. Similar increases in creatine kinase were not seen in subsequent trials.

In Trial PSO2001, the proportions of subjects experiencing markedly abnormal values in hematology and chemistry laboratory test results were low (<5%) among all guselkumab dose groups. There was no adverse impact of treatment with guselkumab on fasting lipid values or glucose over time.

In Trial 3003, the frequencies of abnormalities in hematology and chemistry laboratory values consistent with CTCAE toxicity grade ≥2 were generally low and comparable between the guselkumab and ustekinumab groups from Week 16 through Week 40.

Vital Signs

As part of the evaluation of systemic safety during the core psoriasis trials, subject's vital signs [temperature, resting pulse rate, and blood pressure (BP)] were evaluated.

For Trials 3001 and 3002, normal diastolic BP (DBP) was defined as ≥60 to ≤80 mm Hg and normal systolic BP (SBP) was defined as ≥90 to ≤120 mm Hg. Normal pulse rate was defined

as ≥60 to ≤100 beats/min. Approximately 90% to 95% of subjects in each treatment group with vital sign data at Baseline and Week 16 had a normal pulse rate value at Baseline (90.5%, 94.7%, and 89.8% in the guselkumab, placebo, and adalimumab groups, respectively). Almost all subjects in each treatment group with a normal baseline pulse rate had a normal value at Week 16 (95.2%, 94.2%, and 94.0% in the guselkumab, placebo, and adalimumab groups, respectively). Therefore, treatment with guselkumab did not meaningfully affect pulse rate.

A shift table analysis from Week 0 to 16 demonstrated that only 30% of subjects had a normal baseline value for SBP and only 50% had a normal value for DBP. Approximately 70% of guselkumab, placebo, and adalimumab treated subjects had elevated systolic values at Baseline and approximately 40% of these subjects had elevated diastolic values at Baseline. Approximately 35% of subjects in guselkumab, placebo, and adalimumab treatment groups experienced shifts from a normal baseline value to an elevated value at Week 16 for SBP and 20% of these subjects experienced shifts from a normal baseline value to an elevated value at Week 16 for DBP. Through Week 16 in Trials 3001 and 3002, investigators reported AE of hypertension in 2.6% of subjects in the guselkumab group, 2.6% in the US licensed adalimumab group, and 1.9% in the placebo group. The effect of guselkumab on BP was evaluated by Dr. Karen Hicks from the Division of Cardio-Renal Products (DCARP). In her consult review, Dr. Hicks states that "DCARP does not find the difference in the proportion of treatment emergent adverse events for hypertension to be clinically significant." Furthermore, DCARP does not recommend discussion of hypertension in product labeling.

In Trial 1001, among the 20 subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg, there were no notable mean changes or dose-related trends in vital sign measurements. In Trial 1002, among the 20 Japanese subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg, there were no dose-related changes or clinically significant findings related to vital signs.

In Trial PSO2001, subjects treated with guselkumab 5 to 200 mg SC did not experience any clinically meaningful changes from baseline in BP and pulse rate at Weeks 16 and 52. In Trial 3003, subjects treated with guselkumab 100 mg SC did not experience any clinically meaningful changes from baseline in BP and pulse rate at Week 16 through Week 40.

Electrocardiograms (ECGs)

The applicant conducted ECG monitoring during the development program for guselkumab during all the core psoriasis trials.

In Trials 3001 and 3002, 12-lead ECGs were obtained at Baseline and at Weeks 16 and 48. An evaluation of mean changes from baseline in ECG interval values (heart rate, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval) at Week 16 and Week 48 did not reveal any clinically meaningful changes in posttreatment values in any treatment group. ECG abnormalities reported through Week 16 and Week 48 that were different than those reported at baseline were summarized by treatment group.

For both trials, the percentage of subjects with postbaseline abnormalities through Week 16 in the guselkumab group (7.5% for Trials 3001 and 3002) was consistent with the percentage for the placebo group (7.4% for Trial 3001; 10.0% for Trial 3002). Similarly, the percentage of subjects with postbaseline abnormalities through Week 48 in the guselkumab group (11.1% for Trial 3001; 13.3% for Trial 3002) were consistent with those for the adalimumab group (15.4%

for Trial 3001; 8.8% for Trial 3002). The most common postbaseline abnormalities consisted of conduction abnormalities (mainly first degree AV block) and T-wave abnormalities (mainly flat or inverted T-wave).

In Trial 3003, 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.

In Trial 1001, there were no notable mean changes or dose-related trends in ECG measurements among the 20 subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg. In Trial 1002, there were no trends or dose-related changes in recorded ECG measurements, or clinically significant ECG abnormalities, observed among the 20 Japanese subjects with plaque psoriasis who received a single SC dose of guselkumab 10, 30, 100, or 300 mg.

In Trial PSO2001, an evaluation of mean changes from baseline in ECG interval values (heart rate, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval) at Week 16 and Week 52 did not reveal any clinically meaningful changes from baseline values in any treatment group.

The QT Interdisciplinary Review Team (QT-IRT) concluded that “there is little evidence of a treatment effect for the observed ECG abnormalities”.

Evaluation of the effect of guselkumab on the QT interval will be discussed in the next subsection of this review.

QT

ECG’s performed during the development program for guselkumab and submitted to the ECG warehouse were reviewed by the QT Interdisciplinary Review Team (QT-IRT). Per Dr. Christine Garnett, the QT-IRT reviewer, “The nonclinical and clinical data reviewed do not suggest a potential for QTc prolongation. To further support the clinical assessment, an outlier analysis was conducted, which does not support a potential for QTc prolongation for guselkumab.”
A thorough QT study was not performed for guselkumab. The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Recent publications, however, indicate a consensus that, because of their large size and high target specificity, mAbs such as guselkumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Immunogenicity

A total of 1730 subjects who were enrolled in Phase 2 and Phase 3 trials (PSO2001, Trial 3001, Trial 3002, and Trial 3003) had samples which were evaluable for the presence of anti-drug antibodies (ADA). Among these subjects, 96 developed (5.5%) ADA at any timepoint. In Phase 2, the development of ADA did not correlate with dose. In subjects who had up to 52 weeks of exposure to guselkumab, the majority of antibody titers were low with 79 of 96 samples (79.2%)

being ≤ 1:160. Among the subjects with ADA, 7/96 (7.3%) developed antibodies that neutralized the activity of guselkumab in vitro (neutralizing antibodies, Nabs.) Overall, 0.4% of subjects with evaluable samples had Nabs. The incidence of antibodies to guselkumab in Phase 2 and 3 trials is summarized below.

Table 38: Incidence of Antibodies to Guselkumab in Subjects with Psoriasis in Phase 2 and 3 Trials

Treatment groups[a]	Subjects who received Guselkumab (N)	Subjects with evaluable samples[b] (N)	Incidence of antibodies to guselkumab	Incidence of Neutralizing Antibodies
PSO3001[d]				
Overall	494	492	26 (5.3%)	5 (19.2%)
Placebo→ guselkumab	165	165	7 (4.2%)	
100 mg guselkumab	329	327	19 (5.8%)	
PSO3002[e]				
Overall	873	869	57 (6.6%)	2 (3.5%)
Placebo→ guselkumab	233	231	11 (4.8%)	
guselkumab	494	492	35 (7.1%)	
Adalimumab→ guselkumab	146	146	11 (7.5%)	
PSO3003[f]				
Overall	135	130	4 (3.1%)	0 (0.0%)
Ustekinumab→ guselkumab	135	130	4 (3.1%)	
PSO2001[c]				
Overall	246	239	9 (3.8%)	0 (0.0%)
Placebo→ guselkumab	39	38	0 (0.0%)	
5 mg guselkumab	41	39	1 (2.6%)	
15 mg guselkumab	41	41	3 (7.3%)	
50 mg guselkumab	42	40	2 (5.0%)	
100 mg guselkumab	42	41	0 (0.0%)	
200 mg guselkumab	41	40	3 (7.5%)	
Total	1748	1730	96 (5.5%)	7 (0.4%)

Source: Modified from BLA 761061, Summary of Clinical Pharmacology, Section 4.1.1 Table 20; 4.1.5 Table 24
a Dosing in each study was multiple doses; dose groups include all subjects who received guselkumab at any time.
b Subjects with evaluable and appropriate samples had ≥ 1 samples obtained after their first guselkumab administration.
c Last visit assessed for antibodies: Week 52.
d Last visit assessed for antibodies: Week 44.
e Last visit assessed for antibodies: Week 48.
f Last visit assessed for antibodies: Week 36

In the pooled Phase 3 trials (3001 and 3002), the incidence of ADA 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 was 6.0% (34/562).

Overall, the formation of ADA appeared to have no effect on the efficacy [e.g. 44/54 (82%) ADA positive and 592/765 (77%) ADA negative subjects achieved PASI 90 at Week 28], PK or safety. Although there was a slight imbalance in the number of injections site reactions in the ADA positive group, the development of ADA was not associated with severe administration reactions or hypersensitivity events. In addition, because the number of subjects with ADAs is small, it is difficult to draw a definitive conclusion regarding the potential impact of ADAs on the

clinical efficacy or safety. Due to the limited number of Nabs detected [7 (0.4%)], no analysis of the relationship of Nabs with safety or efficacy was conducted.

Refer to Dr. Anand Balakrishnan's evaluation of the antidrug antibody (or binding antibody) assay and neutralizing antibody assay in Section 6 of this review.

The potential for immunogenicity during treatment with guselkumab is communicated in product of labeling (Section 6.2 Immunogenicity).

7.3.5. Analysis of Submission-Specific Safety Issues

Guselkumab, an interleukin-23 blocker, is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) which is produced in a mammalian cell line using recombinant DNA technology. The applicant identified a set of Adverse Events of Special Interest (AESI) which were based on the mechanism of action (immunomodulation via cytokine blockade), class effects associated with other anti-cytokine antibody therapies and AEs observed with increased frequency in the target population with moderate to severe plaque psoriasis. The categories of AEs which were analyzed as Adverse Events of Special Interest (AESI) were the following: infections, infections treated with oral or parenteral antibiotics (serious infections), injection-site reaction (ISR), malignancies, cardiovascular (CV) events including major adverse cardiovascular events [MACE], anaphylaxis and serum sickness reactions and neuropsychiatric events. The applicant also documented whether treatment with guselkumab resulted in an exacerbation of the severity of plaque psoriasis. The analysis of AESI for the pooled Phase 3 trials (3001 and 3002) is organized by category of AE below.

<u>Infections: Refer to Section 7.3.4, Treatment -Emergent Adverse Events and Adverse Reactions</u>

<u>Serious infections and Infections treated with oral or parenteral antibiotics</u>
In the pooled Phase 3 trials (3001 and 3002), through Week 16, the number of reports of serious infections was similar in the guselkumab group [1 erysipelas (0.1%)] compared with the placebo group [1 chronic cholecystitis (0.2%)] and less than the U.S. licensed adalimumab group [2 cellulitis 2/196 (1.02%)]. Additional reports of serious infections through Week 28 included: 2 subjects in the guselkumab group (bronchitis and soft tissue infection) and 2 subjects in the placebo→guselkumab crossover group (anal abscess and wound infection.)

Through Week 48, the event rate for serious infections was 1.17/100 subj-yrs of follow up (95% CI]: 0.56, 2.16) in the guselkumab group, compared with 0.78/100 subj-yrs of follow up (95% CI: 0.02, 4.33) in the placebo group and 2.12/100 subj-yrs of follow up (95% CI: 0.44, 6.18) in the U.S. licensed adalimumab group. The majority of serious infections were single events (except cellulitis). In subjects treated with guselkumab, there were no reports of tuberculosis or opportunistic infection.

Table 39: Number of Treatment-Emergent Serious Infections per Hundred Subject-Years of Follow-Up through Week 48

	Treatment Group		
	Guselkumab[a]	Placebo	U.S. Licensed Adalimumab[b]
Subjects treated	1221	422	196
Total Sub-yrs of follow up	852	129	142
# Serious infections/ 100 Sub-yrs of follow up	1.17	0.78	2.12
Infection by SOC/PT			
Infections/Infestations			
Abscess	0.12	0.00	0.00
Anal abscess	0.12	0.00	0.00
Appendicitis	0.12	0.00	0.00
Bronchitis	0.12	0.00	0.00
Cellulitis	0.23	0.00	1.41
Erysipelas	0.12	0.00	0.00
Pneumonia staphylococcal	0.00	0.00	0.71
Postop wound infection	0.12	0.00	0.00
Soft tissue infection	0.12	0.00	0.00
Wound infection	0.12	0.00	0.00
Hepatobiliary disorders	0.00	0.78	0.00
Cholecystitis chronic	0.00	0.78	0.00

Source: Adapted from Applicant's TableTSFINFE05C SD 20 page 16
a subjects received only guselkumab or placebo
b subjects received only adalimumab or placebo

Through Week 48, the number of treatment-emergent Infections requiring oral or parenteral antimicrobial treatment per 100 subject-years was 28.17/100 subj-yrs of follow up in the guselkumab group, 26.40/100 subj-yrs of follow up in the placebo group and 29.82/100 subj-yrs of follow up in the U.S. licensed adalimumab group.

Injection-site reaction (ISR)
During the 16 week placebo-controlled period, ISR occurred in 4.5% of subjects in the guselkumab group, compared to 2.8% and 7.7% in the placebo and U.S. licensed adalimumab groups, respectively. ISR are discussed in more detail in section 7.3.4 Safety Results, under Treatment Emergent Adverse Events and Adverse Reactions. ISR will be included in product labeling under adverse reactions section. Through Week 48, the number of ISR was 15.97/100 subj-yrs of follow up in the guselkumab group, 25.62/100 subj-yrs of follow up in the placebo group and 102.26/100 subj-yrs of follow up in the US licensed adalimumab group.

Malignancies
From Weeks 0 – 48 in the pooled safety database, a total of 9 subjects treated with guselkumab, 0 subjects treated with U.S. licensed adalimumab (1 subject treated with EU approved adalimumab) and 0 subjects treated with placebo reported malignancies.

Table 40: Number of Subjects with Treatment-Emergent Malignancies for Weeks 0-48

	Guselkumab[a]	Placebo	Adalimumab U.S. licensed
Total subjects (N)	823	422	196
Non-melanoma skin cancer	6	0	0
Basal cell carcinoma (BCC)	4		
Squamous cell carcinoma (SCC)	2		
Other malignancies	3	0	0
Prostate	2		
Breast	1		

Source: Adapted from Table TSFMAL02C, Integrated Summary of Safety
a Subjects who received guselkumab regardless of whether they crossed over from placebo

Through the Placebo-Controlled Period (Weeks 0-16), there was a single report of a basal cell carcinoma (BCC) in the guselkumab treatment group and no reports of malignancies in the placebo or adalimumab groups. The incidence rate for nonmelanoma skin cancer (NMSC) in the guselkumab treatment group through Week 16 was 0.39/100 subj-yrs [95% CI: 0.01, 2.18].

From Week 16 (Day 112) to Week 28 (196), there was a report of a squamous cell carcinoma (SCC) in the guselkumab treatment group, a BCC in the EU approved adalimumab treatment group and a BCC and SCC in the placebo/guselkumab crossover treatment group. In addition, there were 2 reports of prostate cancer in the guselkumab treatment group. The incidence rate of NMSC through Week 28 in the guselkumab group (0.46 /100 subj-yrs [95% CI: 0.06, 1.65]) was similar to the adalimumab group (rate for combined U.S. licensed and EU approved product was 0.33/100 subj-yrs [95% CI: 0.01, 1.81]).

From Week 28 (Day 112) to Week 48 (Day 336), there was a report of a BCC in the guselkumab treatment group and a BCC in the placebo/guselkumab crossover treatment group. In addition, there was a report of a breast cancer in the guselkumab treatment group.

The overall incidence rate for NMSC through Week 48 was 0.62/100 subj-yrs (95% CI: 0.23, 1.34) in the guselkumab group. This incidence rate was similar to the overall rate for ustekinumab [0.52/100 subj-yrs, (STELARA® (ustekinumab) injection labeling, Section 6.1]. Corresponding event rate for malignancies other than NMSC through Week 48 in the in the guselkumab group was 0.31/100 subj-yrs (95% CI: 0.06, 0.90) compared with 0.60 /100 subj-yrs for ustekinumab [STELARA® (ustekinumab) injection labeling, Section 6.1].

Refer to the table below for a summary of these malignancies by treatment group.

Table 41: Subjects with Treatment-Emergent Malignancies Weeks 0- 48

Treatment Group/ Subject identifier	Study Day of AE (if known)	Study Day 1st dose of Guselkumab	Malignancy	Study Day Final dose of Gus/Ada
Plbo→guselkumab				
CA90210-20873	211	120	BCC-L cheek	148
US01513-20965	142	113	BCC -R shoulder	310
US93366-20454		113	SCC-thumb	143
Guselkumab				
AU00217-10368	310	1	BCC-nasal bridge	309
CA90165-10283	163	1	Prostate cancer	141
US02020-10666	202	1	Breast cancer	197
US02074-10579	56	1	BCC -chest	310
PL00248-20229	130	1	Prostate cancer	138
US91507-20959	112	1	SCC-arm	142

Source: Adapted from Table LSFMAL01, Integrated Summary of Safety
Basal cell carcinoma =BCC
Squamous cell carcinoma =SCC

All of the subjects who developed NMSC were White males with at least 1 risk factor for the development of malignancy. Among the 6 subjects with BCC or SCC, one subject had a personal history and two subjects had a family history of NMSC; three subjects had a history of actinic keratosis, and one subject (who developed an SCC) had a history of UVB treatment. Both subjects who were diagnosed with SCCs were smokers. All subjects who developed BCCs reported treatment with phototherapy or recreational sun exposure. Although these subjects had underlying risk factors, a role for immunosuppression in the development of these malignancies cannot be excluded.

Although NMSC is the most common malignancy in the US, the precise incidence is not known because skin cancers are not generally reported in registries and are treated in an outpatient setting. A recent retrospective analysis of the Medicare database estimates that the incidence of NMSC in the US population in 2012 was greater than 5.4 million (3.3 million patients developed NMSC/313 million total population 2012= ~1%)[14]. Thus, compared to the estimates of risk in the general population, there was no excessive risk of malignancy with guselkumab administration.

Two of the three subjects who developed solid tumors had signs of malignancy prior to receiving guselkumab. One subject (53 year old), who reported prostate cancer had an abnormal prostate specific antigen (PSA) at baseline; the 76 year old male subject who reported breast cancer observed a nodule in his breast for 1 year prior to enrollment in the trial. A comparison of the number of malignancies (other than cervical cancers in situ or NMSC) from Phase 3 trials 3001 and 3002 in the guselkumab group with data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2000-2012[15]; adjusted for age, sex, and race) indicated that the rate of these events in subjects with moderate to severe psoriasis

[14] Rogers HW et al. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the US Population, 2012. JAMA Dermatol. 2015;151(10):1081-1086.
[15] National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 17 Registries, 2000-2012.

treated with guselkumab for up to 48 weeks was no higher than that expected for the general US population [standard incidence ratios (SIR)=0.72 (95% CI: 0.15, 2.11)].

The narratives of subjects who developed malignancies are as follows:

- A 71 year old White male subject (#20873) with Fitzpatrick type I/II skin and recreational sun exposure while golfing developed a BCC on his left check. This adverse event occurred on Study Day 211 after 2 doses of guselkumab (Day 120 and Day 148). Causality was assessed as not related and the subject completed the trial.

- A 61 year old White male subject (#20965) with a history of a BCC on his nose and extensive recreational sun exposure developed a BCC on his right shoulder in an area previously affected with psoriasis. This adverse event occurred on Study Day 142 after 2 doses of guselkumab. Causality was assessed as not related and the subject completed the trial.

- A 64 year old White male subject (#20454) with a history of smoking, a family history of cancer and prior treatment with ixekizumab was diagnosed with a SCC located at the base of the right thumb on approximately Study Day 148 after 2 doses of guselkumab (Day 113 and Day 143). Causality was assessed as doubtful but the subject discontinued the study drug per protocol.

- A 57 year old White male subject (#10368) with a history of “heliotherapy” for psoriasis and actinic keratoses documented at screening developed a nodular BCC on the left-side of the nasal bridge on Study Day 310 after 6 doses of guselkumab. Causality was assessed as possible. This subject also had focal high grade prostatic dysplasia in 1/10 core biopsies on Day 282. Causality was assessed as doubtful.

- A 53 year old male subject (#10283) with a no personal or family history of cancer was diagnosed with prostate cancer on Study Day 163 after 4 doses of guselkumab. The subject had non-study related blood tests drawn which indicated an elevated prostate-specific antigen (PSA) level (9.6 µg/L [normal range < 3.5 µg/L]). When the diagnosis of prostate cancer was reported, the investigator withdrew the subject from treatment. Testing of residual baseline serum for PSA showed an elevated level (10.1 µg/L). Causality was assessed as doubtful.

- A 76 year old White male subject (#10666) with a history of prostate cancer (in remission) developed invasive papillary breast carcinoma on Study Day 202 after 5 doses of guselkumab. Approximately 1 year prior to enrollment in the trial, the subject observed a slowly enlarging sub-areolar, right breast mass which became tender. Pathology results after right modified radical mastectomy showed Grade III invasive ductal carcinoma with micropapillary features with 2 / 6 lymph nodes positive for metastatic carcinoma. Causality was assessed as not related and he discontinued the trial.

- A 37 year old White male subject (#10579) with a history of sunbathing 3 to 4 times per week developed a BCC on his chest on Day 56 after 2 doses of guselkumab. He had no family history of skin cancer. Causality was assessed as doubtful and he completed the trial.

- A 65 year old White male subject (#20229) with a history of chronic prostatitis and prior treatment with acitretin, cyclosporine and methotrexate for psoriasis, developed an

adenocarcinoma of the prostate (total Gleason score 7.) Prostate cancer was diagnosed on approximately Study Day 130 after 4 doses of guselkumab. Causality was assessed as not related and he discontinued guselkumab due to AE at Week 28.

- A 60 year old White male subject (#20959) with a history of smoking, actinic keratosis, sun exposure, treatment with UVB and etanercept developed a SCC of the right arm on Study Day 142 after 4 doses of guselkumab. Causality was assessed as not related and he discontinued guselkumab at Week 20 per protocol.

- A 53 year old White male subject (#10906) who was treated with UVB for psoriasis reported a 3 year history of a non-healing lesion on his left lower leg. On approximately Study Day 128 after 10 doses of **Adalimumab**, a biopsy was obtained which showed a nodular BCC. Causality was assessed as not related and the subject completed the trial.

- See Section 7.3.4 (SAE in Trial 3003) regarding Trial 3003 for the narrative of a female subject who was receiving guselkumab and developed a transitional cell carcinoma following a 6 month history of hematuria.

Cardiovascular (CV) events
In view of the epidemiologic associations between psoriasis and cardiovascular (CV) comorbidities, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the applicant conducted supplemental analyses on all events related to the CV system. In addition, the applicant enlisted a Clinical Events Committee (CEC) to adjudicate potential CV events in the Phase 2 Trial PSO2001 and the three Phase 3 Trials (3001, 3002, and 3003). The CEC adjudicated all fatal events and classified these events as CV or Non-CV.

The applicant defined major adverse cardiovascular events (MACE) as a composite of CV death, nonfatal MI, and nonfatal stroke. The category of “other CV events” included the following: hospitalization for unstable angina (HUA), transient ischemic attack (TIA), venous thromboembolic (VTE) event, peripheral arterial thrombotic event, coronary revascularization (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery), heart failure (HF), arrhythmia requiring intervention, CV-related syncope, and severe/accelerated hypertension leading to hospitalization.

Karen A. Hicks, M.D., Division of Cardiovascular and Renal Products (DCRP), reviewed the data from the 4 Phase 2 and Phase 3 trials and identified 15 MACE events from all treatment groups. The MACE events included the following:

- 1 CV death due to MI (one subject in the guselkumab 5 mg q 12 weeks [q12w] treatment group);
- 12 MIs (5 subjects in the guselkumab, 2 subjects in the ustekinumab to guselkumab [randomized], 1 subject in the placebo to guselkumab, 1 subject in the European Union [EU]-approved adalimumab, 1 subject in the US licensed adalimumab, and 2 subjects in the ustekinumab [1 randomized and 1 non-randomized] treatment groups; and
- 2 ischemic strokes (1 subject in the guselkumab and 1 subject in the non-randomized ustekinumab treatment groups).

Dr. Hicks indicated that the annualized MACE rates from the combined trials were 0.84/100 subject-years (subj-yrs) in the guselkumab group, 0.63/100 subj-yrs in the US licensed

adalimumab group, and 5.08/100 subj-yrs in the ustekinumab group. However, this annualized MACE rate for guselkumab included subjects who did not receive the proposed dose and who received ustekinumab prior to guselkumab treatment.

Trial PSO2001
Through Week 52, there were a total of 3 MACE events: 1 CV death due to MI, 1 MI, and 1 ischemic stroke. Two events (1 MI and 1 stroke) occurred in the guselkumab 100 mg q8w treatment group (MACE rate of 5.00/100 subject-years [subj-yrs]), compared to 1 event (CV death) in the guselkumab 5 mg q12w treatment group (MACE rate of 2.86/100 subj-yrs).

Trial 3001
Through Week 48, there were a total of 2 MACE events: 1 MI in the EU approved adalimumab treatment group and 1 MI in the guselkumab 100 mg treatment group. The MACE rate was 0.34/100 subj-yrs for the guselkumab 100 mg treatment group, 0.25/100 sub-yrs for the all guselkumab treatment group, and 0 for placebo.

Trial 3002
Through Week 48, there were a total of 5 MACE events: 1 MI in the placebo to guselkumab treatment group, 3 MIs in the guselkumab treatment group and 1 MI in the US licensed adalimumab to guselkumab treatment group while the subject was receiving adalimumab. Of the 4 MIs in subjects receiving guselkumab, 1 MI occurred 162 days following the withdrawal of guselkumab (in the placebo to guselkumab treatment group) and the other 3 MIs occurred within 8 weeks of the initiation of guselkumab (range 8 to 52 days). The MACE (MI) rate was 1.37/100 subj-yrs in the placebo to guselkumab treatment group and 0.68/100 subj-yrs in the guselkumab treatment group.

Trial 3003
From Weeks 16 through 40, there were a total of 3 MACE events in the randomized treatment arms, including 2 MIs (1.48%) in the guselkumab treatment group and 1 MI (0.75%) in the ustekinumab treatment group. The annualized MACE rate was 3.23/100 subj-years for the guselkumab treatment group and 3.39/100 subj-yrs for the ustekinumab treatment group.

Other CV events
Among the 15 "other CV events" in Trials 2001, 3001, 3002, and 3003 the following occurred in subjects receiving guselkumab:

- 2 hospitalizations for unstable angina (2 subjects in the guselkumab 100 mg treatment group)
- 1 heart failure event
  - 1 subject in the guselkumab treatment group
- 2 arrhythmias requiring intervention
  - 1 subject in the placebo to guselkumab 100 mg treatment group (sinus node dysfunction requiring permanent pacemaker placement)
  - 1 subject in the randomized ustekinumab to guselkumab 100 mg treatment group while receiving guselkumab (sinus bradycardia due to nebivolol)

The annualized rate of "Other CV Events" for the 4 combined trials was 0.42/100 subj-yrs in the guselkumab group. The annualized rates for MACE and other CV are summarized in the table below.

Table 42: MACE and "Other CV Events" (Trials 2001, 3001, 3002, and 3003 Combined)

	Adalimumab (US)	Adalimumab (EU)	Guselkumab	Ustekinumab
# of subjects treated	217	407	1602	133
Total subject-years of follow-up	159	301	1191	59
MACE				
# of Events (%)	1 (0.46)	1 (0.25)	10 (0.62)	3 (2.26)
100 Subject-Years	0.63	0.33	0.84	5.08
Other CV Events				
# of Events (%)	3 (1.38)	4 (0.98)	5 (0.31)	3 (2.26)
100 Subject-Years	1.89	1.33	0.42	5.08
Analysis by Ququan Liu, MD, MS				

Source: Review by Karen A. Hicks, M.D., DCRP dated 4/17/2017

Dr. Hicks concluded "Based on the available data, at this time we do not observe evidence of a clinically meaningful imbalance in MACE or other CV events with guselkumab." In addition, she stated that "there is no aspect of these findings—MACE or hypertension—that we would mention anywhere in labeling." Refer to the Memorandum by Karen A. Hicks, M.D (dated 4/17/2017) for analyses of the data from individual trials.

Anaphylaxis and serum sickness reactions

To identify subjects who experienced serious hypersensitivity reactions, the applicant conducted a Standard MedDRA Query (SMQ) for anaphylaxis and performed analyses of individual terms (anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, Type I hypersensitivity, and serum sickness or serum sickness-like reaction) and grouped terms for serum sickness (arthralgia, myalgia, fever and rash). This approach was adequate to determine that there were no reports of anaphylaxis or serum sickness reactions in subjects who received guselkumab in the development program. However, a 49 year old, White male developed angioedema on Study Day 5 following a single dose of guselkumab. Angioedema resolved by Day 7 and was assessed by investigators as of "unknown origin" but "possibly related." The subject received a total of 7 doses of guselkumab without recurrence of angioedema or episodes of urticaria.

In subjects receiving guselkumab, the majority of the hypersensitivity reactions were events of "urticaria" which did not result in discontinuation of the study product or withdrawal of the subject from the trial. Among these subjects, there were 3 subjects who experienced urticaria assessed as "reasonably related" to guselkumab in the pooled Phase 3 trials (3001 and 3002). None of the 3 subjects discontinued the study product. However, in Trial PPP2001, a 52 -year- old Japanese male subject (#810901) with moderate to severe palmoplantar pustulosis (PPP) who received guselkumab discontinued treatment after his first dose of guselkumab due to acute urticaria of mild severity. The relationship was assessed as probable.

Therefore, although no serious hypersensitivity reactions were observed in subjects receiving guselkumab, urticaria will be included as adverse reaction (occurred in < 1% but > 0.1%) in Section 6.1 *Clinical Trials Experience* of labeling.

Neuropsychiatric events

Patients with psoriasis have a greater risk of the development of psychiatric disorders than the general population.[16] In order to address the concern that anticytokine therapies may potentiate this risk, the applicant conducted a retrospective analysis of suicidal ideation and behavior (SIB) events using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). In addition, the applicant searched the safety data in the development program for preferred terms suggestive of self-injurious behavior, as described by Posner.[17] The applicant defined a set of adverse events as "potentially suicide-related events" (PSREs) for adjudication by a group of blinded experts. Four board-certified psychiatrists and clinical psychologists reviewed and scored the resulting 321 events.

In the pooled safety analysis set (Trials 3001 and 3002) through Week 48, there was one event of suicidal ideation in the guselkumab group, 2 events of suicide attempt in the adalimumab group (1 receiving U.S. licensed; 1 receiving EU approved) and no events of SIB in the placebo group. The narrative of the subject who received guselkumab is as follows:

- A 39 year old White female (# 21262) with a history of depression and suicidal ideation who refused antidepressant therapy reported suicidal ideation on Day 154 after 4 dose of guselkumab. The event resolved after 3 days. The investigator assessed the event as moderate in severity and possibly related to guselkumab but did not discontinue the study product.

The incidence rate of adjudicated suicidal ideation and behavior (SIB) events based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for the pooled safety analysis set (Trials 3001 and 3002) was 0.10 per 100 subj-yrs in the guselkumab group. There were no reports of SIBs events in any subjects receiving guselkumab in the development program. This rate is similar to other biologic products (secukinumab, 0.06/100 subj-yrs; ixekizumab, 0.14/100 subj-yrs) which effect circulating IL17.

Dr. John Umhau, Division of Psychiatry Products, concluded that applicant provided adequate collection, tabulations, and analyses for the FDA's requested retrospective suicide analyses (C-CASA) for guselkumab in the treatment of patients with psoriasis. He noted that the entry criteria did not exclude subjects with a history of SIB although subjects with a history or presence of signs or symptoms of "severe, progressive, or uncontrolled psychiatric disturbance" were excluded from enrollment. He found no statistically significant risk for SIB associated with guselkumab compared to placebo.

He also stated that review of adverse event data from Trials 3001 and 3002 revealed few psychiatric adverse events and no substantially increased risk of psychiatric events with guselkumab compared to placebo.

[16] Picardi A, Lega I, Tarolla E. Suicide risk in skin disorders. Clin Dermatol. 2013; 31(1):47-56.
[17] Posner, Kelly, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. American Journal of Psychiatry 2007;164(7): 1035-1043

Table 43: Incidence (N(%)) of Non-SIB Psychiatric Adverse Events through Week 16 in Trials 3001 and 3002

Adverse Event	Guselkumab (N=825)	Placebo (N=422)
Anxiety	1 (0.1%)	2 (0.5%)
Depression	1 (0.1%)	0 (0.0%)
Insomnia	1 (0.1%)	0 (0.0%)
Libido Decreased	0 (0.0%)	1 (0.2%)
Psychotic Disorder	1 (0.1%)	0 (0.0%)
Derealization	1 (0.1%)	0 (0.0%)

Source: adapted from review by Dr. John Umhau, page 7

Dr. Umhau concluded that although these data are limited by the small sample size, the small number of SIB events, and the lack of prospective measurement, they do not suggest an increased risk of SIB or psychiatric adverse effects with guselkumab in patients with plaque psoriasis that would justify prominent labeling of suicidal ideation or behavior or other psychiatric adverse events. Dr. Umhau recommended that because currently available pharmacovigilance methods lack sensitivity to detect SIB during the post marketing period, future clinical trials should include a prospective evaluation of suicidal ideation, such as the Columbia-Suicide Severity Rating Scale (C-SSRS). See Review by Dr. John Umhau (dated 4/10/2017).

7.3.6. Safety Analyses by Demographic Subgroups

The review team conducted multiple analyses to evaluate the safety profile of guselkumab in different populations. The results indicated that there were no substantial differences in the risk of adverse reactions in demographic subgroups. However, because the trials were not powered for these analyses, the data must be interpreted with caution. A slightly greater proportion of females who received either guselkumab or placebo reported adverse reactions of upper respiratory infection, headache, injection site reaction, arthralgia and diarrhea than males. Approximately 95% of subjects enrolled in the Phase 3 trials were adults ≤ 64 years of age; therefore, because of the limited number of subjects age >65 years, it would be difficult to detect any differences in safety compared with younger subjects. The data for safety by race is difficult to interpret due to the relatively small sample sizes of the non-White subgroups. The safety findings across the two weight subgroups (≤90 kg and >90 kg) were similar although a greater percentage of subjects in the >90 kg subgroup experienced elevated liver enzymes.
Refer to Appendix 13.3 for the results of the safety analyses by demographic subgroup.

7.3.7. Supportive Safety Data from Other Clinical Trials

The applicant submitted supportive safety data from one Phase 2 dose-range finding trial, 2 Phase 1 trials and 5 additional trials in other indications [palmoplantar pustulosis (PPP), rheumatoid arthritis (RA)] and other patient populations (Japanese subjects only.) A brief description of the study designs and results are provided below.

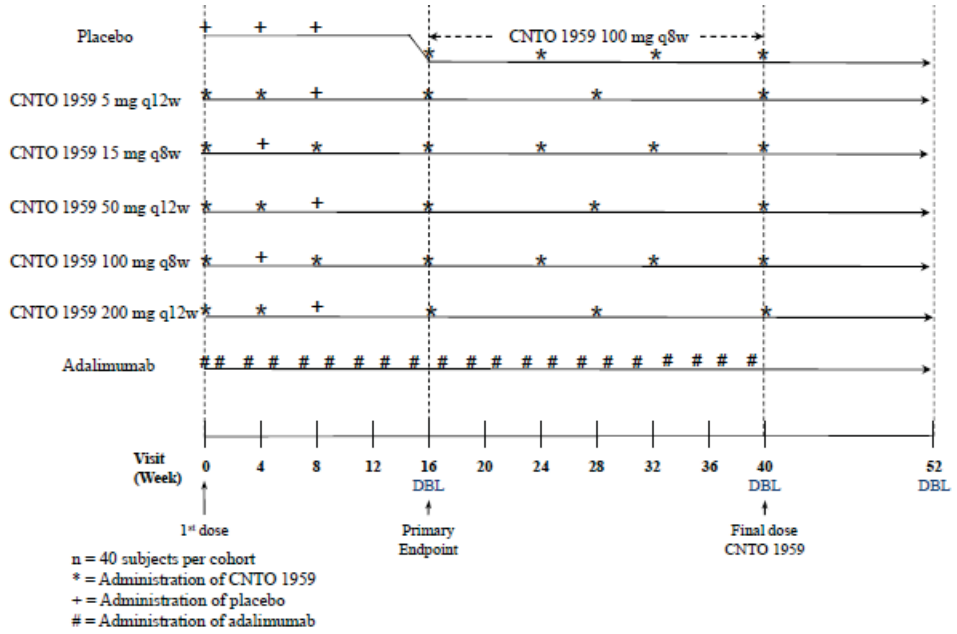
<u>Trial PSO2001</u>
<u>Trial Design</u>
This was a Phase 2, randomized, placebo- and active-comparator (adalimumab) controlled, parallel-group, multicenter (31 sites in North America; 12 sites in Europe), dose-ranging trial.

Study population
The trial enrolled 293 male and female subjects age 18 -82 years (median 45 years) with a diagnosis of moderate to severe plaque psoriasis (PASI score ≥12, PGA score ≥3, and BSA affected ≥ 10%) for at least 6 months prior to the first study drug administration. Subjects may have been treated with phototherapy or some systemic therapies for psoriasis (except adalimumab or guselkumab). This target population was similar to the Phase 3 trials (3001 and 3002). See Section 7.2.1.

Trial procedures
After the 4 week screening phase, eligible subjects were randomized into one of 7 treatment groups in equal proportions:

- Placebo SC (at Weeks 0, 4, and 8 and then guselkumab 100 mg at Week 16 and then once every 8 weeks [q8w]) (42 subjects)
- Guselkumab 5 mg SC (at Weeks 0, 4, and 16 and then once every 12 weeks [q12w]) (41 subjects)
- Guselkumab 15 mg SC (at Weeks 0, 8, and 16 and then q8w) (41 subjects)
- Guselkumab 50 mg SC (at Weeks 0, 4, and 16 and then q12w) (42 subjects)
- Guselkumab 100 mg SC (at Weeks 0, 8, and 16 and then q8w) (42 subjects exposed to the proposed dose)
- Guselkumab 200 mg SC (at Weeks 0, 4, and 16 and then q12w) (42 subjects)
- Open-label adalimumab 80 mg SC (at Week 0, 40 mg at Week 1, and then 40 mg once every 2 weeks [q2w] as per current labeling through Week 39) (43 subjects: 21 used U.S. licensed product and 22 used EU approved product)

All subjects administered guselkumab through Week 40 with a subsequent efficacy and safety follow-up visit at Week 52 as presented in the Schematic Diagram of Study Design below.



Source: BLA 761061, Clinical Study Report CNTO1959PSO2001, Figure 1

The primary assessments of treatment effect were based on PGA, calculated from the average grades for induration, erythema, and scaling on each of three 6-point scales, and PASI. Safety monitoring was similar to the Phase 3 trials and included physical examinations, VS, surveillance for injection and allergic reactions, TB screening, ECGs, clinical laboratory tests, concomitant medications and AEs. Samples were collected for the assessment of guselkumab concentration and the development of anti-drug antibodies (ADA).

The safety data from trial PSO2001 was not pooled with data from Phase 3 trials (3001 and 3002) due to the differences in study designs, doses and dosing regimens (e.g. no loading dose at Week 4 in the guselkumab 100 mg group).

Efficacy endpoints
The primary efficacy endpoint was the proportion of subjects who achieved a score of 0 ("cleared") or 1 ("minimal") on PGA at Week 16. The first major secondary endpoint was the proportion of subjects treated with guselkumab who achieved PASI 75 response at Week 16. The applicant investigated PASI 90 response at Week 16 and 0 ("cleared") or 1 ("minimal") on PGA and PASI 75 through Week 52 as "other secondary endpoints."

Financial disclosure
Two investigators [Howard Sofen (Site 0017) and Alexandra Kimball (site 0020)], disclosed financial arrangements with the applicant in excess of $25,000 on Financial Disclosure Forms 3455. See Appendix 13.2.

Subject Disposition
Among the 293 subjects, 208 subjects were randomized to the guselkumab groups, 42 subjects were randomized to the placebo group, and 43 subjects were randomized to the adalimumab group. A total of 21 subjects received the U.S. licensed product.

Table 44: Subject Disposition through Week 52: Adalimumab (U.S. Licensed), Placebo and Guselkumab (CNTO 1959)

		CNTO 1959							
	Adalimumab (US-Licensed)	Placebo → 100 mg q8w[a]	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined[b]	All CNTO 1959[c]
Subjects randomized	21	39	41	41	42	42	42	208	247
Subjects who discontinued study agent[d]	8 (38.1%)	2 (5.1%)	12 (29.3%)	4 (9.8%)	5 (11.9%)	3 (7.1%)	7 (16.7%)	31 (14.9%)	33 (13.4%)
Reason for discontinuation									
Adverse event	2 (9.5%)	1 (2.6%)	1 (2.4%)	0	1 (2.4%)	1 (2.4%)	5 (11.9%)	8 (3.8%)	9 (3.6%)
Worsening of psoriasis	0	0	0	0	0	0	0	0	0
Lack of efficacy	3 (14.3%)	0	5 (12.2%)	0	0	0	1 (2.4%)	6 (2.9%)	6 (2.4%)
Lost to follow-up	2 (9.5%)	0	2 (4.9%)	0	1 (2.4%)	1 (2.4%)	0	4 (1.9%)	4 (1.6%)
Withdrawal of consent	1 (4.8%)	0	1 (2.4%)	0	2 (4.8%)	0	0	3 (1.4%)	3 (1.2%)
Death	0	0	1 (2.4%)	0	0	0	0	1 (0.5%)	1 (0.4%)
Pregnancy	0	0	0	0	0	0	0	0	0
Other	0	1 (2.6%)	2 (4.9%)	4 (9.8%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	9 (4.3%)	10 (4.0%)

Source: Applicant's Table TSIDS01B, SD 16 dated 2/21/2017, page 14
a Only includes subjects who were crossed over to receive CNTO1959 100 mg q8w.
b Including CNTO 1959 treatment columns (5 mg q12w, 15 mg q8w, 50 mg q12w, 100 mg q8w, and 200 mg q12w).
c Including all CNTO 1959 treatment columns (Placebo → 100 mg q8w, 5 mg q12w, 15 mg q8w, 50 mg q12w, 100 mg q8w, and 200 mg q12w).
d Includes subjects who were randomized but not treated.

Overall Exposure

Through Week 52 the average number of injections received by subjects treated with the proposed dose of guselkumab (100 mg q8w) was 5.7 with a median total dose of 600 mg. In contrast, subjects treated with the highest dose of guselkumab (200 mg q12w) received an average of 4.7 injections and a median total dose of 1000 mg.

Table 45: Subject Exposure through Week 52: Adalimumab (U.S. Licensed), Placebo and Guselkumab (CNTO 1959)

			CNTO 1959					
	Adalimumab (US-Licensed)	Placebo → 100 mg q8w[a]	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined
Subjects treated	21	39	41	41	42	42	41	246
Avg number of CNTO1959/adalimumab administrations	16.52	3.92	4.39	5.71	4.71	5.71	4.68	4.87
Total dose								
N	21	39	41	41	42	42	41	246
Mean (SD)	701.0 (257.87)	392.3 (35.43)	23.0 (9.07)	85.6 (12.66)	235.7 (40.25)	571.4 (106.58)	933.8 (169.61)	373.7 (322.64)
Median	880.0	400.0	25.0	90.0	250.0	600.0	1000.0	250.0
Range	(160; 880)	(200; 400)	(10; 70)	(45; 90)	(100; 250)	(100; 600)	(400; 1000)	(10; 1000)
IQ range	(560.0; 880.0)	(400.0; 400.0)	(20.0; 25.0)	(90.0; 90.0)	(250.0; 250.0)	(600.0; 600.0)	(1000.0; 1000.0)	(90.0; 600.0)

Source: Applicant's Table TSFEXP01C, SD 16 dated 2/21/2017, page 15
a Only includes subjects who were crossed over to receive CNTO 1959 100 mg q8w

Deaths

There was one death reported through Week 52. A subject with multiple cardiovascular risk factors died of a myocardial infarction.

- A 55 year old obese White male (# 0103-0206) from Canada with a history of smoking and alcohol use who developed hyperlipidemia while receiving guselkumab (5 mg q12w X 3 doses) and experienced a myocardial infarction (MI) on Day 194. He had no prior history of coronary artery disease (CAD), MI, diabetes (DM), hyperlipidemia or hypertension (HTN), and had no family history of early CAD. He died in the ICU on Day 208 after progressive deterioration of his status. The association with guselkumab was assessed as possible.

Serious Adverse Events (SAEs)

Through Week 16, 3 subjects (1.4%) in the combined guselkumab groups (5mg q12w, 15mg q8w, 50 q12w, 100 q8w and 200 mg q12w), 1 subject (2.4%) in the placebo group, and 1 subject (#0011-00159) in the U.S. licensed adalimumab group (2.3%) reported one or more SAEs. In the guselkumab group, all 3 subjects reporting SAEs received 50 mg q 12w and their narratives are as follows:

- A 56 year old White female (#0009-00130) with a history of smoking, alcohol use and infliximab and methotrexate therapy for psoriasis developed acute appendicitis on Day 77 after 2 doses of guselkumab (50 mg q 12w). The subject recovered after treatment with antibiotics and laparoscopic appendectomy .The association with guselkumab was assessed as not related and the subject completed the trial (3 doses of guselkumab).

- A 47 year old White male (# 0404-00162) with a history of smoking and methotrexate, cyclosporine and acitretin therapy for psoriasis developed a lung abscess on Day 85 after 2 doses of guselkumab (50 mg q 12w). A QuantiFERON test was negative and there was no growth of acid-fast mycobacteria. CT scan and chest radiographs confirmed that the abscess resolved with treatment with multiple antibiotics. The association with guselkumab was assessed as possibly related.

- A 28 year old White female (#0401-00348) with a history of methotrexate therapy for psoriasis who weighed 78 kg developed an umbilical hernia on Day 28 after 2 doses of guselkumab (50 mg q 12w). After surgical intervention, the incarcerated umbilical hernia resolved. The association with guselkumab was assessed as not related and the subject completed the trial (3 doses of guselkumab).

From Week 16 to Week 52, 5 subjects experienced at least 1 SAE (1 subject in the EU approved adalimumab group (#0103-00247) had multiple SAEs; 2 subjects in the 5 mg q12w guselkumab group, and 2 subjects in the 100 mg q8w guselkumab group). Therefore, through Week 52, a total of 7 subjects (3.4%) in the combined guselkumab groups reported one or more SAEs compared with 1 subject (2.4%) in the placebo group, and 2 subjects in the combined adalimumab groups (4.7%). There were 2 reports of myocardial infarction but all other reports of SAEs were single events. The narratives of subjects in the guselkumab groups who experienced SAEs from Week 16 to Week 52 are as follows:

- A 69 year old obese White female (#0108-00393) from Canada with a history of smoking, anxiety and gastroesophageal reflux disease (GERD) experienced a MI on Day 248 after 5 doses of guselkumab 100 mg q8w. The subject had no history of CAD, MI, DM, hyperlipidemia, or HTN and no family history of early CAD. She had a critical proximal left anterior descending (LAD) artery lesion which was treated with a drug-eluting stent. The relationship to guselkumab was assessed as doubtful and she received a 6th administration of guselkumab.

- A 55 year old obese White male (# 0103-0206) experienced a MI on Day 194. See narrative above.

- A 70 year old White female (# 0022-00193) from the US with a history of hypertension, hyperlipidemia, hyperthyroidism and atrial fibrillation (noted at baseline) experienced an ischemic stroke on Day 292 after completing treatment with guselkumab (100 mg X 6 doses). She had no history of DM or hyperlipidemia and no family history of early CAD. ECGs during treatment demonstrated intermittent first-degree atrioventricular block (AVB) and sinus bradycardia. A magnetic resonance imaging (MRI) scan of the brain revealed subacute right parietal and occipital lobe infarcts and an old left occipital infarct. Echocardiogram indicated no obvious cardiac source of embolization. This event was assessed as possibly related.

- A 43 year old White male (#0200-00334) with a history of osteoarthritis who was using metamizole sodium for pain experienced a worsening of arthrosis of the left shoulder joint on Day 195 after 4 doses of guselkumab (5 mg q12w). He was hospitalized and underwent left shoulder joint replacement. The association with guselkumab was assessed as not related and the subject completed the trial (1 dose of guselkumab).

Adverse Events Resulting in Drug Discontinuation
Through Week 16, 5 subjects (2.4%) in the combined guselkumab groups and 3 subjects each in the placebo group (7.1%) and adalimumab group (2 receiving U.S. licensed product and 1 receiving EU approved product) (7.0%) discontinued the study product due to one or more adverse events. In the combined guselkumab groups the adverse events which resulted in drug discontinuation were thrombocytopenia, lung abscess, hepatic enzyme increased, nerve

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compression and dermatitis psoriasiform. Selected narratives regarding the subjects who received guselkumab are as follows:

- 52 year old obese White male (#-0015-00106) with a history of smoking and alcohol use (21 servings per week) and no concomitant medications experienced thrombocytopenia on Day 28 after one dose of guselkumab (100mg q8w.) The investigator suspected that the cause was alcohol abuse and the association with guselkumab was assessed as not related. The platelet level normalized by Week 8 (Day 56).

- 32 year old obese White male (#0025-00007) with a history of methotrexate and etanercept therapy for psoriasis developed elevated liver enzymes on Day 44 after 2 doses of guselkumab 200 mg q12w. Per protocol, at screening the subject initiated isoniazid (INH) as treatment for latent tuberculosis evidenced by a positive QuantiFERON test result. The investigator attributed the liver enzyme elevations to INH based on the positive dechallenge and rechallenge to the drug.

- 48 year old White male (#0404-00141) developed a persistent, pruritic dermatitis and concomitant laboratory abnormalities (elevated liver enzymes, eosinophilia, elevated white blood cell and neutrophil counts) on Day 89 after2 doses of guselkumab 200 mg q12w. Biopsy demonstrated a psoriasiform reaction pattern. Physical examination showed coalescing erythematous, scaly papules with exudate and crusting. Although the laboratory abnormalities normalized, the eruption did not resolve with systemic antihistamines, phototherapy, topical corticosteroid ointment, and emollients. The diagnosis was not established and association with guselkumab was assessed as not related.

Through Week 52, 8 subjects (3.9%) in the combined guselkumab groups and 4 subjects each in the placebo group (7.1%) and U.S. licensed adalimumab group (9.3%) discontinued the study product due to one or more adverse events. In the combined guselkumab groups the adverse events which resulted in discontinuation after Week 16 were myocardial infarction, cervical dysplasia (CIN III) and arthralgia. Myocardial infarction and cervical dysplasia are discussed under adverse events of special interest. The third narrative is as follows:

- 61 year old obese White female (#0301-00125) with a history of psoriatic arthritis and anticipated knee replacement surgery experienced arthralgia on Day 123 after 3 doses of guselkumab 5 mg q12w. She discontinued the study drug due to her pending surgery. The association with guselkumab was assessed as not related.

Treatment Emergent Adverse events (TEAEs)
The proportion of subjects reporting TEAE was 49.8% in the combined guselkumab groups compared with 52.4% in the placebo group. There was no evidence of dose related increase in adverse events (AE). The most frequently reported system organ class (SOC) was Infections and infestations (20.3% of the combined guselkumab group; 14.3% of the placebo group) followed by Musculoskeletal and connective tissue disorders (8.2% for combined guselkumab; 11.9% for placebo group) and Injury, poisoning and procedural complications (7.2% of the combined guselkumab group; 0% of the placebo group.) Through Week 16, the most common AE (≥1% of subjects and greater than placebo) in the combined guselkumab groups were nasopharyngitis (6.8%), headache (4.8%), and upper respiratory tract infection (3.4%), back pain (2.9%) and hypertension (2.9%).There was a similar distribution of AEs through Week 52 with the addition of arthralgia, gastroenteritis, sinusitis, cough and muscle strain observed in

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greater than 1% of subjects. The distribution and the proportion of subjects reporting of TEAEs were similar to the Phase 3 trials.

Adverse Reactions (AR)
The most common AR were observed in the Infections and infestations and the General disorders and administration site conditions SOCs. The preferred terms which were reported with greater frequency in the guselkumab group than the placebo group and occurred in more than 1 subject were: nasopharyngitis / upper respiratory tract infection [15 (7.2%) of the combined guselkumab group compared to 1 (2.6%) of the placebo group] and injection site reactions which include erythema, induration, pain, pruritus and swelling [7 (3.4%) of the combined guselkumab group vs 0 in the placebo group], fatigue [3 (1.4% of the combined guselkumab group vs 0 in the placebo group] and headache [2 (1.0%) of the combined guselkumab group vs 0 in the placebo group.]

Laboratory and ECG Results
There were no clinically significant ECG abnormalities or changes in laboratory parameters including lipid levels.

Adverse events of special interest through Week 52

Major adverse cardiovascular event (MACE)
There were 3 MACE reports through Week 52 in subjects with multiple cardiac risk factors.

- 70 year old White female (# 0022-00193) with a history of atrial fibrillation noted at baseline experienced a stroke on Day 292 after completing treatment with guselkumab (100 mg X 6 doses). See narrative above.

- 69 year old White female (# 0103-00206) with a history of smoking and a BMI of 30.5 reported a MI on Day 248 after 5 administrations of guselkumab (100 mg q8w). See narrative above.

- 55 year old obese White male (# 0103-0206) experienced a MI on Day 194 which resulted in death. See narrative above.

Malignancy
- A 31 year old White female (#0011-00202) who developed cervical intraepithelial neoplasia III on Day 287 after administration of 5 doses of 200 mg of guselkumab. The association with guselkumab was assessed as doubtful.

Hypersensitivity reactions
- There were no acute or delayed-type hypersensitivity reactions reported.

Opportunistic infection
- Among subjects treated guselkumab, there were no reported cases of tuberculosis. However, 2 subjects discontinued the trial due to INH hepatotoxicity which was administered due to a positive QuantiFERON test result at screening.

Serious infections requiring hospitalization/antibiotics
- There were two cases of serious infections [appendicitis on Day 77 in a 56 year old female after 5 doses of guselkumab 100 mg (assessed as not related) and lung abscess on Day 85

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in a 47 year old male with a history of smoking and methotrexate therapy after 2 doses of guselkumab 50 mg (assessed as possibly related.)] See narratives above.

Pregnancy
- There were no maternal pregnancies and 1 paternal pregnancy in the guselkumab group (15 mg q8w). The subject did not consent to provide outcome information.

Worsening of psoriasis
- One subject exposed to guselkumab (5 mg q12w) reported a worsening of psoriasis.

Suicidal ideation and behavior (SIB) Events
- The applicant identified "potentially suicide-related events" (PSREs) during the trial which were referred for adjudication. The adjudicated events were all classified as non-suicidal events (not SIB events). See Psychiatry Review dated 4/10/2017 for a discussion of the adverse events in the psychiatric disorders SOC (i.e. Insomnia, anxiety, depression) which were observed with guselkumab.

Antibodies to guselkumab
- Among 240 subjects with evaluable samples, a total of 15 subjects who were treated with guselkumab developed ADA (5.1%). None of these subjects with positive antibody titers developed injection site reactions while 4 of the subjects with negative antibody titers developed injection site reactions (1.8%).

Phase 1 Trials PSO1001 and PSO1002
The applicant conducted 2 Phase 1, randomized, double-blind, placebo-controlled, and ascending single-dose trials.

- Trial PSO1001: In Part 1, 47 healthy subjects age 18 to 50 years were randomized to one of 6 cohorts to receive IV administration of single doses of guselkumab (0.03 , 0.1, 0.3, 1, 3, or 10 mg/kg) or placebo. In addition, 7 subjects were randomly assigned to a single SC dose of 3 mg/kg of guselkumab or placebo. In Part 2, 24 subjects age 20 to 62 years with moderate to severe plaque psoriasis (defined as BSA ≥ 10%, PASI ≥ 12) were randomized to 4 cohorts of 6 subjects to receive SC administration of single SC doses of guselkumab (10, 30, 100, and 300 mg) or placebo. Subjects were evaluated for safety (physical examinations, laboratory tests, vital signs, ECGs and AE), pharmacokinetics, pharmacodynamics, pharmacogenomics, immunogenicity and efficacy.

  Safety Results
  There were no deaths or AEs leading to study drug discontinuation but 1 subject with psoriasis experienced a serious AE of traumatic brain injury secondary to a motor vehicle accident (unrelated). In both parts, the system-organ class with the most frequently reported AEs was "Infections and Infestations". In Part 1, the most common AEs were headache (9/36 [25.0%] subjects on guselkumab and 3/11 [27.3%] subjects on placebo) and upper respiratory infection (5/36 [13.9%] subjects on guselkumab and 1/11 [9.1%] subjects on placebo). In Part 2, the most common AEs were upper respiratory tract infection and vomiting (each in 2/20 [10.0%] subjects on guselkumab and none in subjects on placebo). With regard to the AEs of special interest, a 57 year old male subject with a history of hypertension and MI who was enrolled in Part 2 and received guselkumab (10 mg) experienced tachycardia for ≥ 8 hours after administration; 1 subject in Part 2 experienced

an injection site reaction. No trends or dose related changes in vital signs, physical examinations, ECGs, or laboratory values were observed.

- Trial PSO1002: 24 Japanese subjects age 33 to 64 years with moderate to severe plaque psoriasis (defined as BSA ≥ 10%, PASI ≥ 12) were randomized into 4 sequential cohorts of 6 subjects to receive single SC doses of guselkumab (10, 30, 100, and 300 mg) or placebo. Subjects were evaluated for safety, pharmacokinetics, pharmacodynamics, pharmacogenomics, immunogenicity and efficacy.

  Safety Results
  There were no deaths, SAEs, or AEs leading to study agent discontinuation. A total of 11/20 (55.0%) subjects receiving guselkumab and 2/4 (50.0%) subjects receiving placebo experienced one or more AEs. Infections were observed in 4 /20 (20.0%) subjects receiving guselkumab (3 subjects in the 10 mg group [folliculitis, sinusitis, upper respiratory tract inflammation and nasopharyngitis] and 1 subject in the 100 mg group [folliculitis and nasopharyngitis]) compared to none in the subjects receiving placebo.

  The most common AE (≥2 subjects) was pruritus, followed by folliculitis, nasopharyngitis, and injection site erythema. Injection site reactions were observed in 2/20 (10.0%) subjects receiving guselkumab (1 subject each in the 10 and 300 mg groups [injection site erythema]) compared to none in the subjects receiving placebo. Two subjects had a transient increase in creatine kinase (CK)[1 subject in the 100 mg group experienced mild muscle spasms at Week 8 and 1 subject in the 300 mg group experienced mild myalgia at Week 2.] No trends or dose related changes in vital signs, physical examinations, ECGs, or laboratory values were observed.

The safety profile indicated by these single dose trials was similar to the Phase 3 trials and provided no new safety signals.

Safety data from the Phase 1, single- dose trials in the psoriasis development program, PSO1001 and PSO1002, were not included in the pooled analyses due to the small sample sizes, different study populations and widely varying doses. Only 10 subjects from PSO1001 and PSO1002 with moderate to severe psoriasis received the proposed 100 mg dose as a single administration.

Conclusions
In addition to the safety data submitted from the Phase 3 trials, the applicant included data from a Phase 2 dose ranging trial (PSO 2001) and 2 Phase 1 PK trials (PSO1001, PSO1002) and supportive safety data from 5 trials which evaluated guselkumab in different populations or different indications (NAP1001, NAP1002, PPP2001,ARA2001, & PSO30050). In 4 of these trials subjects received a single dose of guselkumab (PSO1001,PSO1002, NAP1001 &NAP1002); in 1 trial, subjects received 2 doses (PPP2001) and in 3 trials subjects received multiple doses. The numbers of subjects receiving guselkumab from trials are included in the following table.

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Table 46: Number of Subjects Receiving Guselkumab in Trials Providing Supportive Data

Study population	Plaque psoriasis	Healthy Volunteers	GPP/EP	Rheumatoid arthritis	PPP	Total # receiving any product
PSO2001	250					293 including 43 adalimumab
PSO1001	20	36				71 including 15 placebo
PSO1002	20 Asian					24 including 4 placebo
NAP1001		141				141
NAP1002		8				8
PPP2001					25 Asian	49 including 24 placebo
ARA2001				109		274 including 55 placebo & 110 ustekinumab
PSO3005			21 Asian			21
Total # receiving guselkumab	290	185	21	109	25	

Source: Reviewer's Table
EP=Erythrodermic psoriasis
GPP= generalized pustular psoriasis
PPP=palmoplantar pustulosis

In these trials, a total of 630 subjects were randomized to guselkumab and provided safety data. Among the subjects receiving guselkumab, there was 1 death (0.16%, MI in PSO2001) and 18 SAEs (2.9%). SAEs reported by these subjects included 2 spontaneous abortions, 3 malignancies (gastric cancer, Stage 1 breast cancer, squamous cell carcinoma), 5 serious infections (pyelonephritis, lobar pneumonia, gastroenteritis, appendicitis, lung abscess), 3 MACE events (2 MI, 1 stroke), 3 injuries, 1 worsening arthrosis and 1 umbilical hernia. There were no reports of TB or opportunistic infections; there were no reports of hypersensitivity reactions or anaphylaxis although one subject discontinued guselkumab due to urticaria. The MedDRA system-organ class with the most frequently reported AEs were Infections and Infestations. Infections (URI, nasopharyngitis & herpes simplex) and injection site reactions (erythema & pain) were among the most common adverse events in the majority of the trials, even those including a single administration. Refer to Appendix 13.3 for additional information.

7.3.8. Additional Safety Explorations

120 Day Safety Update

No new safety signals were identified in the 120 Day Safety Update (SD 21 dated 3/16/2017). The applicant submitted safety data for Phase 3 Trials 3001 and 3002 from Week 48 through October 31, 2016, for Trial 3003 (Week 40 - 60) and for PSO1003, PSA2001, PSO3004, and PSO3005. The focus of this submission was the following key safety events which occurred in subjects receiving guselkumab: deaths, SAEs, AEs resulting in discontinuation of study agent, serious infections, serious MACE, malignancies, serious hypersensitivity reactions, and events of suicidal ideation and behavior.

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Deaths

Among subjects receiving guselkumab in the development program, 5 deaths occurred after Week 48 through October 31, 2016: myocardial infarction, malignancy (squamous cell carcinoma of the neck and brain tumor), suicide, and diabetic coma. Narratives regarding the myocardial infarction (PSO2001), squamous cell carcinoma (Trial 3001) and suicide (Trial 3003) were provided in Section 7.3.4 of this review. Limited information was available regarding the other 2 deaths which occurred after the reporting date (October 31, 2016), brief narratives are provided below:

- **Trial 3001**: A 65 year old male subject (#10671) with a history of psoriasis, diabetes and hyperuricemia, was receiving open label guselkumab (previous dose within 30 days) and experienced dizziness and disorientation. A brain tumor was identified by CT scan on Day 560. Final diagnosis and treatment course prior to death were not available. This AE is assessed as not related.

- **Trial 3002**: A subject with a history of diabetes experienced diabetic coma resulting in death. No other information is provided.

Serious Adverse Events

Trial 3001: A total of 23 subjects receiving open label guselkumab experienced SAEs between Week 48 and October 31, 2016. No subjects experienced MACE. The majority of SAEs were single events which are listed below by treatment group:

- Placebo → guselkumab: unintended pregnancy; hypotension; scrotal abscess; uterine polyp; thrombophlebitis superficial.
- Guselkumab: sudden death (completed suicide); pulmonary embolism; erysipelas; brain neoplasm; chondromalacia; lateral patellar compression syndrome; femoral neck fracture; endometrial polyp, uterine fibroids; gout; pancreatitis.
- Adalimumab → guselkumab: malignant melanoma in situ; suicidal ideation; papillary cystadenoma lymphomatosum; abortion missed; hernia; abdominal injury; chest injury, craniocerebral injury, fracture (x2), humerus fracture, and soft tissue injury, all in 1 subject; chronic tonsillitis; basal cell carcinoma (BCC); post procedural complication; skin infection (right first metatarsal head) due to fissure.

Trial 3002: A total of 37 subjects reported SAEs. Because the randomized withdrawal and retreatment period began at Week 28 and extended through Week 72, not all subjects were receiving guselkumab at the time of the SAE. The majority of SAEs were single events which are listed below by treatment group:

- **Subjects originally randomized to placebo**
  Subjects with SAEs during
  - withdrawal (n=3): psoriatic arthropathy; craniocerebral injury; adenoma benign.
  - retreatment (n=2): pneumonia; pilonidal cyst.
  - continuing guselkumab (n=2): hypertension; chronic sinusitis.
- **Subjects originally randomized to guselkumab**
  Subjects with SAEs during
  - withdrawal (n=5): erysipelas; retinal vein occlusion and psoriatic arthropathy (2 events in 1 subject); anemia; hemorrhoidal hemorrhage; MI.

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  - retreatment (n=5): irritable bowel syndrome; peritonsillar abscess; pulmonary embolism; paresthesia; MI.
  - continuing or open-label guselkumab (n=12): musculoskeletal chest pain; myocardial infarction with left anterior descending artery (LAD) occlusion; radius fracture; muscular weakness; alcoholism; cellulitis (2 subjects); cystitis; pneumonia; spinal cord injury cervical; vaginal hemorrhage (2 events in 1 subject); appendicitis.
- **Subjects originally randomized to adalimumab**
  - Subjects with SAEs during initial or open-label guselkumab (n=7): anxiety; atrial fibrillation; peripheral nerve paresis; rectal cancer; bradycardia; angina unstable; dysuria.

Selected narratives

- 57 year- old -male (#20393) with a history of diet-controlled type 2 diabetes mellitus, dyslipidemia, and family history of coronary heart disease and thromboembolism, was hospitalized with chest pain with shortness of breath on Day 362. Troponin (x3) and a Doppler scan of both legs were negative. An ECG showed sinus tachycardia with flattened T waves in lateral leads. A CT scan confirmed bilateral pulmonary emboli. The subject was started on rivaroxaban and IV morphine for chest pain. This event was not related.

- 46 year- old -female (#20970) with a history of hypertension and hyperlipidemia, experienced ischemic branch retinal vein occlusion of the left eye and was emergently hospitalized. Slit lamp examination showed right and left eye cataract with no further findings. Fluorescein angiogram of the retina showed left eye of the retina showed left eye neovascularization of papilla with leakage, ischemic area superior of papilla. This event was not related.

- 42 year- old -male (#10392) with a history of smoking experienced pain and swelling in the right inguinal area and was hospitalized with a right inferior superficial epigastric vein thrombosis. The thrombotic epigastric vein was successfully resected. This event was not related.

Trial 3003:
The proportions of randomized subjects who reported SAEs from Week 16 through Week 60 were 6.7% (n=9) in the guselkumab group and 4.5% in the ustekinumab group (n=6). Among nonrandomized subjects receiving ustekinumab from Week 16 through Week 60, 3.4% (n=20) experienced 1 or more SAEs. Most of the reported SAEs were single events. The PT reported by more than one subject receiving guselkumab was myocardial infarction. There were 2 pregnancies among subjects receiving guselkumab with outcomes of spontaneous abortion and ectopic pregnancy. Refer to Section 7.3.4 for narratives of SAEs for subjects receiving guselkumab up to Week 40, the remaining narratives from Week 40 to Week 60 are as follows:

- 37 year old female (#30653) with a history of smoking, PsA and prior surgical debridement and partial synovectomy of her right elbow, developed septic arthritis of her right knee and elbow on Day 368 after receiving 5 doses of guselkumab. The subject reported a 2-year history of worsening right knee and right elbow pain and stiffness. She was hospitalized after experiencing acute pain, swelling and immobility **of her** right knee and right elbow and treated with one dose of vancomycin, daily intravenous (IV) ceftriaxone and azithromycin. Synovial fluid analysis (after vancomycin) was negative for bacteria and her rheumatologist

assessed this event as a potential flare of PsA vs septic arthritis. The diagnosis was not confirmed and this event was possibly related.

- 31 year old Asian male (#30726) with a history of smoking reported a spontaneous abortion in his partner on Day 372 after receiving 5 doses of guselkumab. **Reproductive history was not provided.** The event of spontaneous abortion was probably not related to guselkumab but insufficient information was provided.

- 41 year old (#30671) developed a complicated migraine on Day 394 after receiving 3 doses of guselkumab. The subject was lost to follow up and no other information was provided.

SAEs in subjects receiving guselkumab from other trials included: **MI** (PSA2001, see narrative below), colon adenoma and rectal adenocarcinoma (PSO3004), bacterial prostatitis (PSO3004) and SCC of the skin (PSO3004). Narratives will be included for these events in other parts of this review.

No trends in the pattern of SAEs were observed in the Phase 3 trials.

Adverse Events Resulting in Discontinuation of the Study Product

In Trial 3001 from Week 48 through October 31, 2016, 3 subjects receiving guselkumab discontinued the study product due to AEs. In the guselkumab group, one subject developed a brain tumor; in the adalimumab → guselkumab group, one subject reported psoriatic arthropathy and one subject reported a pregnancy/missed abortion. In Trial 3002 from Week 48 through October 31, 2016, 2 subjects receiving guselkumab discontinued the study product due to AEs. In the placebo → guselkumab group (during withdrawal), 1 subject reported psoriatic arthropathy; in the continuous guselkumab group, 1 subject developed prostate cancer. Events such as malignancies and pregnancy required discontinuation of the study product per protocol. Narratives regarding malignancies are below.

In other trials, AEs which resulted in discontinuation of the study product included: toxicity to various agents, psoriatic arthropathy, transitional cell carcinoma (Trial 3003), viral gastroenteritis /impaired gastric emptying, pregnancy (PSO1003), mild leukopenia /neutropenia (PSA2001), colon adenoma/ rectal adenocarcinoma, pregnancy, hepatitis B reactivation (not confirmed)(PSO3004) (b) (4) (PSO3005.)

Malignancies

In Trials 3001 and 3002, a total of 8 malignancies were reported in subjects receiving guselkumab from Week 48 through October 31, 2016. There were 4 NMSC: 3 in the guselkumab group (3 subjects with BCC) and 1 in the adalimumab → guselkumab group (BCC). There were 4 other malignancies: 2 in the guselkumab group (brain tumor, prostate cancer) and 2 in the adalimumab → guselkumab group (malignant melanoma in situ and rectal cancer). The following are brief narratives of these malignancies:

Adalimumab → Guselkumab: 59 year- old- female (#10296) with a history of actinic keratosis, Fitzpatrick skin type 2 and outdoor employment and recreation, developed a BCC on her right nasal bridge. BCC was not related.

Guselkumab: 68 year- old- male (#20178) developed a BCC of the left pre-auricular area. No other information is available but the BCC was assessed as not related.

Guselkumab: 72 year- old- male (#20261) with a history of BCC of the left lower eyelid, fair skin, and outdoor recreation, developed a BCC of the left lower eyelid. BCC resolved with treatment and was assessed as not related.

Adalimumab → Guselkumab: 66 year- old- male (#20589) with no history of skin cancer developed a superficial BCC localized to an area previously affected with psoriasis. The BCC resolved with treatment and was assessed as not related.

Adalimumab → Guselkumab: 43 year old male (#10408) with a history of substantial sun exposure and fair skin (Fitzpatrick type 1) developed a new pigmented lesion on his right ear. Biopsy showed a melanoma in situ which was successfully excised with clear margins. Malignant melanoma in situ was assessed as not related.

Adalimumab → Guselkumab: 57 year old male (#20806) was hospitalized for rectal carcinoma which was locally invasive into the bladder. The neoplasm was successfully resected and the event was reported as resolved. Rectal carcinoma was assessed as not related.

Guselkumab: 63 year old White male (#10594) with a history of diabetes, obesity, hyperuricemia and previous treatment with infliximab, methotrexate, ustekinumab and UVB, developed a brain tumor on Day 560. He was hospitalized with complaints of dizziness and disorientation and CT scan showed a brain tumor. The applicant was informed that the subject had died but other information was not provided. The relationship with guselkumab was assessed as doubtful.

Guselkumab: 68 year- old- male (#21017) with hypertension was diagnosed with adenocarcinoma of the prostate on approximately day 390. No metastatic disease was evident on CT scan or bone scan. No other information was provided. The subject withdrew from the trial due to this AE. Prostate cancer was assessed as possibly related.

The rate of malignancy from Week 48 through October 31, 2016 in subjects who received only guselkumab or placebo was 0.65 events/100 subject-years. Based on biologic plausibility, exposure to guselkumab may contribute to the development of malignancy in subjects with or without risk factors. Refer to Section 12 Postmarketing Requirements and Commitments for the proposal to characterize the malignancy risk associated with the use of guselkumab.

Serious Infections

During the reporting period, there were no opportunistic infections or cases of active TB among the serious infections. In Trial 3001, 3 subjects who received guselkumab reported serious infections: scrotal abscess (placebo → guselkumab group), erysipelas (guselkumab group) and skin infection of the right first metatarsal head (adalimumab → guselkumab group).In Trial 3002, 8 subjects who received guselkumab had serious infections during the reporting period: pneumonia (in 2 subjects), erysipelas, peritonsillar abscess, cellulitis (in 2 subjects), cystitis, and appendicitis. All subjects were originally randomized to placebo or guselkumab. Among all subjects who received guselkumab through Week 48, the rate of serious infections was 0.98 events/ 100 subject -years. In Trial 3003, one subject receiving guselkumab experienced a

serious infection, bacterial arthritis. The event occurred on Day 368, more than 8 weeks after his last dose, and was considered possibly related.

Major Adverse Cardiovascular Events

In Trial 3002 from Week 48 to October 31, 2016, there were 3 additional MACE events in subjects receiving guselkumab. Acute MI were reported in 2 subjects in the guselkumab group (one during withdrawal and the other during retreatment), and MI with left anterior descending coronary artery (LAD) occlusion was reported in 1 subject who received continuous guselkumab treatment. The narratives are as follows:

47 year old male (#20267) with a history of smoking and alcohol use was hospitalized with chest pain and diagnosed with an inferior wall MI. Coronary angiography confirmed two-vessel disease with 40% to 50% stenosis of the LAD and 80% to 90% stenosis of the RCA. The event resolved with angioplasty of the RCA and the implantation of a drug-eluting stent. The MI was assessed as doubtfully related.

- 53 year old male (#20346) with a history of smoking, hypertension and obesity was hospitalized with diaphoresis and mild chest pain. He experienced ventricular fibrillation and cardiac arrest but developed spontaneous rhythm and positive perfusion after defibrillation(X 5). Cardiac catheterization was performed and 2 drug-coated stents were placed in the LAD for 100%proximal occlusion and 70 % mid- occlusion. The anterolateral MI was assessed as not related.

- 65 year old female (#20899) with a history of arterial hypertension, type 2 diabetes mellitus, hypothyroidism, dyslipidemia and percutaneous coronary intervention of the LAD in June 2015, was diagnosed with non-ST-elevation myocardial infarction (NSTEMI) and acute coronary syndrome. Angiogram showed a visible stent in the LAD with 40% restenosis and left circumflex with 99% stenosis. The subject was successful treated with percutaneous coronary angioplasty of the left circumflex coronary artery with the implantation of an antimitotic drug-eluting stent. NSTEMI was assessed as possible related.

The event rate for MACE in the pooled Phase 3 trials (3001 and 3002) among subjects receiving only guselkumab during this period was 0.39 events per 100 subj-yrs. Dr. Karen Hicks reviewed the cases of MACE and concluded that there was no evidence of a clinically meaningful imbalance in MACE or “Other CV Events” with guselkumab. (Review by Dr. Karen Hicks dated 4/17/2017).

Other cardiovascular AEs included unstable angina (adalimumab→ guselkumab, #20995), atrial fibrillation (adalimumab→ guselkumab, #20133), bradycardia (adalimumab→ guselkumab, #21096), hypertension (placebo→ guselkumab, # 20075) and hypotension (placebo→ guselkumab, # 10965).

In other trials, there was 1 MACE event in Trial PSA2001. A 48 year old White male with a history of smoking, peripheral vascular disease, hypertension, hyperlipidemia, obesity, atherosclerosis, and carotid endarterectomy, was hospitalized with chest pain on Day 96 and diagnosed with an inferior wall MI. He was treated with coronary stent placement and continued in the trial. The AE was assessed as not related.

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Hypersensitivity Reactions

There were no reports of anaphylaxis or serum sickness in any trial during this reporting period.

Suicidal Ideation and Behavior

In Trial 3001 from Week 48 to October 31, 2016, there was a completed suicide which was discussed in Section7.3.4. The event rate for SIBs in the pooled Phase 3 trials (3001 and 3002) among subjects receiving only guselkumab during this period was 0.13 events per 100 subject-years. This case was reviewed by John C. Umhau MD, Medical Officer from the Division of Psychiatry Products (DPP) who stated that this event is not likely to be related to guselkumab based on "the classical understanding of cytokine effects on mood and impulsivity." (Review by John C. Umhau MD, dated 4/10/2017.)

Human Reproduction and Pregnancy

Requirements for females of childbearing potential who were enrolled in guselkumab development program included the use of effective forms of contraception, negative pregnancy tests at screening and urine pregnancy testing at all study visits. Subjects who became pregnant withdrew from treatment and, where feasible, were followed until delivery. Pregnancy outcomes such as spontaneous abortion, stillbirth, and congenital anomalies were reported as SAEs. In addition, because the applicant did not evaluate the effect of the study drug on sperm, they also reported pregnancies in partners of male subjects who were included in the trials.

Among subjects receiving guselkumab in the development program through October 31, 2016, there were 12 pregnancies, 5 maternal pregnancies and 7 partner pregnancies. Two healthy volunteers reported spontaneous abortions and one subject with psoriasis reported a missed abortion. Among the partners of subjects with psoriasis, there was 1 live birth, 1 spontaneous abortion and one ectopic pregnancy. Outcome data is not available for the remaining pregnancies [6/12 (50%)].

The information that will be conveyed in labeling (Section 8.1 Pregnancy and Section 8.2 Lactation) regarding the risks of exposure to guselkumab during pregnancy and lactation is presented in Section 5.6 of this review. Refer the review (dated 4/12/2017) by Leyla Sahin, M.D., Division of Pediatric and Maternal Health, for recommendations regarding labeling for Section 8.1 Pregnancy and 8.2 Lactation and post marketing requirements to evaluate the risks of exposure to guselkumab during pregnancy and lactation.

We recommend that the applicant propose a pharmacovigilance plan to evaluate pregnancy outcomes in a cohort of women exposed to guselkumab compared to an unexposed control population. Refer to Section 12 Postmarketing Requirements and Commitments.

Human Carcinogenicity or Tumor Development

As large proteins, monoclonal antibodies are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. Guselkumab will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this risk may be potentiated

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by prior exposure to other immunosuppressive agents or other therapies that my enhance tumor development such as phototherapy.

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of guselkumab. Refer to Section 5.5.3 for a discussion of the carcinogenicity risk from a Pharmacology/Toxicology perspective.

Data from the nonclinical and clinical development programs does not support the conclusion that chronic administration of guselkumab is associated with increased risk of carcinogenesis. However, the limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency periods such as malignancy. Therefore, post marketing data are needed to evaluate the long term risk of malignancy in patients with psoriasis receiving guselkumab.

Pediatrics and Assessment of Effects on Growth

The applicant has not conducted an evaluation of the safety and efficacy of guselkumab in the pediatric population.

Because the proposed product is a new molecular entity, approval of guselkumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the applicant submitted an initial Pediatric Study Plan (iPSP) on June 6, 2014 (within 60 days of the End of Phase 2 (EOP2) Meeting).

The Division discussed the proposed iPSP with the Pediatric Review Committee (PeRC) on July 30, 2014. PeRC and the Division agreed with the general plan for the development of guselkumab in the pediatric population but determined that it was premature to agree to a specific trial design at that time. (b) (4) The Division conveyed their agreement with the proposed iPSP on November 21, 2014.

In this submission, the applicant requested a partial waiver for studies in the pediatric population from birth to less than 6 years of age as "Necessary studies are impossible or highly impracticable because the number of patients in these age groups is small" (Section 505B (a)(4)(B)(i) of the Act). Although the epidemiologic data is limited regarding the pediatric population with moderate to severe plaque psoriasis, the prevalence of plaque psoriasis generally increase with age. In addition, the sponsor requested a deferral of studies in the pediatric population from age 6 years to <18 years "until additional safety or effectiveness data have been collected in adults (Section 505B (a)(3)(A)(ii) of the Act)."

In the discussion with PeRC (3/15/2017) regarding the evaluation of guselkumab in the pediatric population, the Division conveyed their agreement with the proposed pediatric development program in the Agreed iPSP. PeRC concurred with the Division but recommended that the applicant modify the timeline for submission of the protocol to 10/2017 (b) (4) .

Refer to Section 9 for the pediatric study requirement for guselkumab under PREA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
In the development program, there were no AEs of overdose of guselkumab.
In the event of overdosage, patients should be monitored for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately. This recommendation will be conveyed in the product labeling (Section 10 OVERDOSE).

Drug Abuse Potential/ Withdrawal and Rebound
There is no data to support an association of monoclonal antibodies including guselkumab with the potential for addiction, abuse, withdrawal or rebound. Therefore, the applicant did not evaluate abuse potential.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Guselkumab is not marketed in any jurisdiction. Therefore, postmarketing safety data is not available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the guselkumab safety data identified no safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of guselkumab in the postmarket setting. However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant and lactating females and the pediatric population age ≥ 6 years) and assess the risk of adverse events associated with long latency periods (malignancy). Refer to Section 12 of this review for the postmarketing requirements and commitments.

7.3.10. Integrated Assessment of Safety

The safety profile for guselkumab was adequately characterized during the drug development program. The primary safety database consisted of subjects from the Phase 3 Trials 3001 and 3002 (the pooled safety analysis set). All subjects treated with guselkumab in the pooled safety analysis set received the proposed dose of 100 mg SC at Weeks 0 and 4, then every 8 weeks thereafter; 1367 subjects received at least 1 injection of guselkumab. Of these 1367, 1036 subjects were treated for 6 months, and 592 subjects received treatment for 1 year.

The review of the safety data did not reveal any contraindications to treatment with guselkumab, and the applicant proposed no contraindications for inclusion in Section 4 of product labeling.

Treatment with guselkumab did not appear to increase risk of mortality. A total of 5 deaths occurred in subjects treated with guselkumab across the 6 primary trials in the development program. Per the applicant, two were assessed as possibly related to treatment (a 55 year old male with MI in Trial PSO2001 and a 67 year old male with squamous cell carcinoma in Trial 3003). Per the applicant, two were assessed as not related (a 43 year old male enrolled in Trial 3001 who committed suicide, and a 65 year old male with a brain tumor in Trial 3001). Assessment of relationship to treatment was not provided for one subject (subject had history of diabetes and died of diabetic coma, Trial 3002- this occurred after the reporting date for the 120 day safety report and no further information was available). Deaths are described in more detail

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in sections 7.3.4 and 7.3.8 of this review. Also, treatment with guselkumab was not associated with an increased incidence of AE in the categories of SIB and MACE. SIB and MACE are discussed in more detail in Section 7.3.5 of this review.

In the pooled safety analysis set from Week 0-16, SAEs occurred in 1.9% of subjects in the guselkumab group, 1.4% of subjects in the placebo group, and 2.6% of subjects in the US licensed adalimumab group. From Week 0-28, SAEs occurred in 3.4% of subjects in the guselkumab group, 3.1% of subjects in the placebo group, and 2.6% of subjects in the US licensed adalimumab group. From Week 0-48, SAEs occurred in 3.9% of subjects in the guselkumab group, 1.4% of subjects in the placebo group, and 3.6% of subjects in the US licensed adalimumab group. SAEs are described in more detail in sections 7.3.1.4 of this review.

In the pooled safety analysis set, the most common adverse reactions (AR) were upper respiratory infections (14.3%), headache (4.6%), injection site reactions (4.5%), arthralgia (2.7%), elevated liver enzymes (2.6%), diarrhea (1.6%), gastroenteritis (1.3%), tinea infections (1.1%), and herpes simplex infections (1.1%). The frequency of AR was similar across all age and demographic groups. These are discussed in more detail in section 7.3.4 of this review. These AR will be included in Section 6 (Adverse Reactions) of guselkumab labeling.

Because of the mechanism of action of guselkumab, malignancy is a potential risk. Out of 823 subjects in pooled safety analysis set for guselkumab, there were 6 cases of non-melanoma skin cancer, 2 cases of prostate cancer, and 1 case of breast cancer through Week 48. Malignancies are discussed in more detail in Section 7.3.5 of this review. Although these data are not sufficient to identify a safety signal, the risk of malignancy is biologically plausible and may exhibit a long-latency effect after initial exposure.

Consultants from the Office of Surveillance and Epidemiology (OSE) evaluated the sufficiency of the Active Risk and identification Analysis system (ARIA) to address the long-term risk of malignancy. ARIA is considered to be sufficient to assess risk for short-term lymphoma, because lymphomas are reasonably well-validated in claims data, short-term risk is of interest, and the other domains (population, exposure, covariates, and analytic tools) were determined to be sufficient. However, ARIA is determined to be insufficient to assess long-term malignancy (i.e., all types), due to limited long-term follow-up, poor validation of certain malignancy types, and incomplete capture of potentially critical confounders. A long-term observational study would be a more appropriate post-marketing study design to better assess malignancy risk among guselkumab users; a Post-Marketing Requirement (PMR) will be recommended through the Division of Epidemiology I to request such a study.

As discussed in section 7.3.8 of this review, through the 120-day safety review cutoff (10/31/2016), there were 12 pregnancies, 5 maternal pregnancies and 7 partner pregnancies. Two healthy volunteers reported spontaneous abortions and one subject with psoriasis reported a missed abortion. Among the partners of subjects with psoriasis, there was 1 live birth, 1 spontaneous abortion and one ectopic pregnancy. Outcome data is not available for the remaining pregnancies [6/12 (50%)]. Because the available data is limited regarding use of guselkumab in pregnant women, the Division of Pediatric and Maternal Health (DPMH) recommends a PMR that requires the applicant to perform a pregnancy exposure registry study and a complementary study to assess the safety of guselkumab in pregnant women.

The safety data currently available demonstrate that guselkumab is safe for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy

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or phototherapy. Postmarketing risk management will include professional labeling (including a Medication Guide), prescription status and routine pharmacovigilance. In addition, the ARIA system will be used to assess the risk of lymphoma over the short term. The long-term risk of malignancy will be assessed by a long-term observational study. The maternal, fetal, and infant outcomes of women exposed to guselkumab during pregnancy will be evaluated by a registry based observational exposure cohort study.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across trials and endpoints. The amount of missing data was relatively small (< 5%) at Week 16 (i.e., the primary efficacy timepoint). For the handling of missing data, the statistical reviewer conducted an additional sensitivity analysis under the worst case scenario (i.e., missing data for guselkumab was imputed as non-responders and missing data for placebo was imputed as responders). In this extreme case, guselkumab remained statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in all both pivotal trials (Trials 3001 and 3002).

There were no substantial differences in efficacy among subgroups. Approximately 94% and 96% of subjects were 18 to 64 years of age in Trials 3001 and 3002, respectively; therefore, it would be difficult to detect any differences in efficacy between this subgroup and its complement (i.e., ≥ 65 years). For gender, the treatment effect was slightly larger in males compared to females for IGA score of 0 or 1 in both trials; however, this was due to a larger placebo response rate in females compared to males. For PASI 90, the treatment effect was larger in males in Trial 3001; however, the treatment effect was larger in females in Trial 3002. For race, the treatment effect was generally consistent; however, it should be noted that the sample size for some of the non-White subgroups (i.e., Black and Other) were relatively small. In both trials, the treatment effect on IGA score of 0 or 1 was consistent across the two weight subgroups (≤90 kg and >90 kg); however, for PASI 90, the treatment effect was larger in the ≤90 kg subgroup in both trials. The treatment effect was generally consistent across the baseline IGA score subgroups and the prior use of systemic therapy subgroups.

7.4.2. Conclusions and Recommendations

To establish the effectiveness of guselkumab, the applicant submitted data from two randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (Trials 3001 and 3002). The trials enrolled subjects 18 years of age and older who had plaque psoriasis with PASI score ≥ 12, IGA score of at least 3 (moderate) and BSA involvement ≥ 10%. The co-primary efficacy endpoints were the proportion of subjects achieving a achieving a IGA score of 0 (“cleared”) or 1 (“minimal”) with at least a 2-point improvement from baseline at Week 16 and the proportion of subjects achieving PASI 90 at Week 16. In both trials, guselkumab was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints at Week 16 (see Table 21 in Section 7.2.1.4).

Trials 3001 and 3002 included adalimumab as an active comparator. In both trials, all subjects randomized to adalimumab in the North American sites (i.e., US and Canada) received US licensed Humira (adalimumab). Subjects randomized to adalimumab at all other sites received EU approved adalimumab. As the applicant did not provide an adequate scientific bridge

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between US licensed Humira and EU approved adalimumab, these products are considered distinct products for the purpose of this review. The results, which include investigator-reported major secondary efficacy endpoints for both the overall population (i.e., all sites) and the North American subgroup are presented in Section 7.2.1.5. In both trials, guselkumab was statistically superior to adalimumab for all of investigator-reported major secondary efficacy endpoints in the overall population (p-values < 0.001) and in the North American subgroup (p-values ≤ 0.027), which included the proportion of subject achieving an IGA score of 0 or 1 at Week 16 and a PASI 90 response at Week 16 (i.e., the co-primary efficacy endpoints).

The applicant conducted a comprehensive assessment of the safety of guselkumab in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Submitted safety and efficacy data support approval of this BLA for guselkumab for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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8 Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile was expected to be similar to that of other biologic products approved for this indication.

9 Pediatrics

Refer to the following sections of this review for the proposed development program for guselkumab in the pediatric population:

- Section 9 *Pediatrics and Assessment of Effects on Growth* for a discussion regarding the Pediatric Study Plan
- Section 12 *Postmarketing Requirements and Commitments* for the deferred pediatric studies, which are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

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10 Labeling Recommendations

10.1. Prescribing Information

The applicant submitted proposed Prescribing Information (PI) and carton/container labels for TREMFYA (guselkumab) injection. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient package insert (PPI), Medication Guide (MG) and carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Silvia Wanis, PharmD, CPH (dated 4/21/2017). In addition, Carlos M Mena-Grillasca, RPh. from the Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the proposed carton and container labels (Review dated 5/15/2017). Labeling negotiations are currently ongoing.

The following table provides the location of the labeling discussion for each section.

Summary of Significant High level Labeling Changes	
Section	**Location of Reviewer Comments on Proposed Labeling**
1 INDICATIONS AND USAGE	Section 1.1, 5.6
2 DOSAGE AND ADMINISTRATION	Section 6.9
4 CONTRAINDICATIONS	Section 7.3 Integrated Summary of Safety
5 WARNINGS AND PRECAUTIONS	Section 7.3.1.4
6 ADVERSE REACTIONS	Section 7.3.1.4
7 DRUG INTERACTIONS	Section 6.3
8 USE IN SPECIFIC POPULATIONS	Section 5.6
12 CLINICAL PHARMACOLOGY	Section 6.6
14 CLINICAL STUDIES	Section 7
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

10.2. Patient Labeling

The applicant submitted a proposed patient package insert (PPI). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the PPI for Tremfya (guselkumab) injection, for subcutaneous use. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN (dated 4/21/2017) for comments regarding the Medication Guide (MG) and Instructions for Use (IFU).

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11 Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and a Medication Guide are not warranted at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 10.1 Labeling Recommendations. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

12 Postmarketing Requirements and Commitments

Clinical postmarketing requirements are intended to characterize the risks of guselkumab use in special populations and address the long- term safety of this novel biologic product in the target population. Development of final pharmacovigilance plans is ongoing. Agreed postmarking quality commitments are summarized in this section and discussed in Section 4.2.5.3.

Guselkumab triggers the Pediatric Research Equity Act (PREA) as a new active ingredient. The following studies in the pediatric population age 6 years to less than 18 years of age were included in the Agreed iPSP and will be deferred:

(b) (4)

[redacted]

The available safety data regarding guselkumab use during pregnancy is limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant or breastfeed during the trials. The applicant reported that 21 pregnancies occurred in female subjects exposed to guselkumab or in female partners of male subjects exposed to guselkumab during the development program for plaque psoriasis, rheumatoid arthritis, or palmoplantar pustulosis. However, no outcome information was available in more than half of these cases. Because human IgG antibodies are known to cross the placental barrier and exposures to guselkumab during pregnancy are likely to occur, the applicant will be required to conduct the postmarketing assessments described below to characterize the drug associated risk.

Based on review of the data in this submission, the following postmarketing requirements (PMRs) and commitments (PMCs) were conveyed to the applicant:

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POSTMARKETING REQUIREMENTS UNDER 505(o)

PMR 1:
A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to guselkumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR 2:
Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to guselkumab during pregnancy compared to an unexposed control population.

PMR 3:
Conduct an observational study to assess the long-term safety of guselkumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to guselkumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the guselkumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial (b) (4) year period and follow for a minimum of 8 years from the time of enrollment.

(b) (4)

REQUIRED PEDIATRIC ASSESSMENTS: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

[redacted] (b) (4)

We are deferring submission of pediatric studies for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The required study is listed below.

Conduct a pharmacokinetics (PK), safety and efficacy study in pediatric subjects 6 years to <18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

At the time of this review, final milestone dates were under discussion. Refer to the Approval Letter for the final PMRs with milestone dates.

POSTMARKETING COMMITMENTS

1. Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

2. Provide additional data comparing the [redacted] (b) (4) Include the [redacted] (b) (4) in the [redacted] (b) (4) revalidation program if the new information indicates that the [redacted] (b) (4).

   Refer to Section 4.2.5.3 regarding the PMCs.

13 Appendices

13.1. References

The majority of the references are included in footnotes.

13.2. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for guselkumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trial 3001, Trial 3002 and Trial 3003 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 7.2.1 and 7.2.2 for the trial designs.

Covered Clinical Study: 3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 115		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Investigators with Financial Disclosure Forms 3455 for Trial 3001

Investigator	Site	Country	# Subjects Randomized	Description of Disclosure
(b) (6)		USA	(b) (6)	Honoraria for sponsored dinner talks > $25,000 at initial collection.
		USA		Payments >$25,000 for consultations, ad board, and lectures not related to guselkumab at initial collection
		USA		Payments for speaking engagements/ consulting > $25,000 at initial collection
		USA		Fellowship funding ~$50,000 (4/2011 - 3/2012) Steering committee payments for PSOLAR of $10,000 at initial collection.
		Canada		Honoraria for lectures, ad board /conference attendances compensation > $25,000 from 2014-2016 at 1 year post trial completion collection
		Canada		Speakers fees, ad board compensation and consulting fees > $25,000 at 1 year post trial completion collection
		USA		Receipt of consulting fees of $28,170.64 since the beginning of trial at 1 year post trial completion collection
		Germany		Honorarium for speaker tours, advisory boards, and consulting fees > $25,000 at interim collection

*Rationale or steps taken to minimize bias: No investigator with a disclosure enrolled/ randomized more than 20 patients in this study.

Covered Clinical Study: 3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 101		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Investigators with Financial Disclosure Forms 3455 for Trial 3002

Investigator	Site	Country	# Subjects Randomized	Description of Disclosure
(b) (6)		USA	(b) (6)	Honoraria for sponsored dinner talks > $25,000 at initial collection.
		Canada		Speaker's Bureau/consulting/ad board fees > $25,000 at initial collection
		Canada		Advisory board meetings/ consultation /speaker fees > $25,000 at interim collection
		Germany		Honorarium for speaker tours, advisory boards, and consulting fees > $25,000 at interim collection
		Canada		Project and honoraria fees > $25,000 at interim collection

***Rationale or steps taken to minimize bias:** No investigator with a disclosure enrolled/randomized more than 20 patients in this study.

Covered Clinical Study: 3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 100		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Investigators with Financial Disclosure Forms 3455 for Trial 3003

Investigator	Site	Country	# Subjects Randomized	Description of Disclosure
(b) (6)		USA	(b) (6)	Honoraria for sponsored dinner talks >$25,000 at initial collection.
		Canada		Honorarium for Ad Boards, CME sessions, sponsorship for international meetings and injection services at interim collection
		Canada		Honoraria for speaking > $25,000 at interim collection
		USA		Payments > $25,000 for consultations, ad board, and lectures not related to guselkumab at initial collection.

***Rationale or steps taken to minimize bias**: No investigator with a disclosure enrolled/randomized more than 17 patients in this study.

The applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

13.3. Clinical/Biostatistics

1) Scales Used to Evaluate Efficacy

Figure 21: Investigator Global Assessment (IGA) scale

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)
0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, > 1 mm

Erythema (E) (averaged over all lesions)
0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration

Scaling (S) (averaged over all lesions)
0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = severe; thick, scale predominates

Total Average = (I + E + S) / 3 (average will be calculated in the device but not displayed. Numeric result will be included in data transfer)
Investigator's Global Assessment based upon above Total Average
0 = Cleared, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1
2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3
4 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 4
Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score = 1; if total ≥ 1.50, score = 2.

Source: protocols for Trials 3001 and 3002 (Attachment 1)

Figure 22: Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

$$PASI = 0.1\,(Eh + Ih + Sh)\,Ah + 0.3\,(Et + It + St)\,At + 0.2\,(Eu + Iu + Su)\,Au + 0.4\,(El + Il + Sl)\,Al$$

Where E = erythema, I = induration, S = scaling, and A = area

Source: protocols for Trials 3001 and 3002 (Attachment 2)

Table 47: Scalp Specific Investigator's Global Assessment (ss-IGA)

Score	Category	Description
0	Absence of Disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp
1	Very Mild Disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild Disease	The overall clinical picture consists of lesions with mild erythema, slight, but definite, thickness, and a thin scale layer
3	Moderate Disease	The overall clinical picture consists of lesions with moderate erythema, a moderate thickness, and a moderate scaled layer
4	Severe Disease	The overall clinical picture consists of lesions with bright erythema, severe thickness and a severe, coarse thick scale layer

Source: protocols for Trials 3001 and 3002 (Attachment 3)

2) Trials Providing Supportive Safety Data

The applicant submitted data from 5 trials conducted during the development program for guselkumab for other indications or in other patient populations. A total of 304 enrolled subjects were exposed to guselkumab (149 healthy volunteers, 25 subjects with palmoplantar pustulosis (PPP), 21 subjects with generalized pustular psoriasis (GPP, 10 subjects) or erythrodermic psoriasis (EP, 11 subjects), 109 subjects with rheumatoid arthritis (RA)).

Trial NAP1001: 141 healthy male and female subjects age 18 to 55 years received a single dose of guselkumab (100 mg SC). The objective of the trial was to evaluate the pharmacokinetic (PK) comparability of lyophilized (40 subjects) and liquid formulations [delivered by a prefilled syringe (b) (4) Delivery System (PFS (b) (4) 40 subjects) or prefilled syringe (b) (4) (PFS (b) (4) 41 subjects)] compared with IV administration (20 subjects). Assessments were conducted for 12 weeks.

Safety Results
There were no deaths or discontinuations due to AEs. Two subjects (1 subject exposed to the lyophilized formulation and 1 subject exposed to the liquid formulation administered IV) reported SAEs of spontaneous abortion during the trial which were considered "reasonably related to the study agent." Neither the 26 -year- old subject (#103045) nor the 38- year- old subject (#103029) had maternal risk factors for spontaneous abortion.

The liquid formation delivered SC by the PFS (b) (4) device resulted in higher systemic exposure (18% to 20%) compared to the PFS (b) (4) and was associated with a greater percentage of adverse reactions related to both the drug and the device (PFS (b) (4) group: 58.5% and 43.9% respectively; PFS (b) (4) group: 52.5% and 17.5%, respectively.)

Overall, the most frequently reported TEAEs were headache (18.4%), injection site erythema (14.2%), nausea (9.2%), induration and cough (each reported by 6.4% of subjects), injection site pain, erythema, and pruritus (each reported by 5.7% of subjects), and feeling hot, dizziness postural, myalgia, and oropharyngeal pain (each reported by 5.0% of subjects). A total of 12 subjects (8.5%) reported treatment-emergent AEs in the Infections and Infestations SOC. The majority of the infections were in the PFS (b) (4) and PFS (b) (4) groups. The most commonly reported infections (2 subjects each) were oral herpes, upper respiratory tract infection and urinary tract infection.

Trial NAP1002: 8 healthy subjects age 26 to 49 years received a single IV infusion of guselkumab at 10 mg/kg over 60 minutes. The objective of this Phase 1, open-label trial was to characterize the elimination of guselkumab glycoform variants. Assessments were conducted for 85 days.

Safety Results
There were no deaths, SAEs or discontinuations due to AEs during the trial. The most frequently reported TEAEs (occurring in at least 2 subjects) were: headache (5 subjects [62.5%]), oropharyngeal pain (3 subjects [37.5%]), upper respiratory tract infection (2 subjects [25%]), and musculoskeletal pain (2 subjects [25%].

Trial PPP2001: 49 Japanese subjects age 28 to 77 years with moderate to severe palmoplantar pustulosis (PPP) who had an inadequate response to conventional therapy were randomized to receive guselkumab 200 mg SC (25 subjects) or placebo (24 subjects) at Week 0 and 4. The

objective of the trial was to assess efficacy, PK and immunogenicity. Assessments were conducted for 24 weeks.

Safety Results
There were no deaths. However, 2 (8.0%) subjects treated with guselkumab reported SAEs (pyelonephritis and gastric cancer) and 1 (4.2%) subject treated with placebo reported an SAE (pustular psoriasis). A 52 -year- old male subject (**#810901)** in the guselkumab group with a history of allergic rhinitis and GERD and multiple concomitant medications discontinued treatment after his first dose of guselkumab due to acute urticaria of mild severity. (Relationship assessed as probable). On Day 75, he presented to the hospital with a 1 month history of anorexia and was diagnosed with gastric cancer (Stage IA). (Relationship assessed as doubtful.)

Infections were observed in 13 (52.0%) of 25 subjects treated with guselkumab and 14 (58.3%) of 24 subjects treated with placebo. The most commonly reported infection was nasopharyngitis (7 [28.0%] subjects treated with guselkumab and 7 [29.2%] subjects treated with placebo). Injection site reactions were observed in 3 (12.0%) of 25 subjects treated with guselkumab and 1 (4.2%) of 24 subjects treated with placebo. Injection site erythema occurred in 2 subjects on guselkumab and in 1 subject on placebo. Other adverse events (≥5% of subjects in any treatment group) seen with greater frequency with guselkumab than placebo were headache, dermatitis contact, and injection site erythema.

Trial ARA2001: 274 subjects with active rheumatoid arthritis (RA) who were treated with concomitant methotrexate were randomized to receive SC placebo, ustekinumab (90 q8w or q12w after a loading dose at Week 4) or guselkumab (50 mg q8w or 200 mg q8w after a loading dose at Week 4) to Week 28 with a safety evaluation at Week 48. Concomitant use of stable low doses of oral corticosteroids (prednisone ≤10 mg/day) and nonsteroidal anti-inflammatory drug (NSAIDs) or other analgesics were permitted.

Safety Results
There was one death in the ustekinumab group. A 61 year old female (#5351) experienced hypovolemic shock, bradycardia, hypotension, hypoxia, and altered consciousness 16 days after the last dose of ustekinumab 90 mg (Day 108); the precise cause of death is unknown because no autopsy was performed(causality assessed as doubtful). There were 3 SAEs in the guselkumab 200 mg group including the following:

- 62 year old White female (#5220) with no family history of cancer reported Stage 1 breast cancer 3 months following the end of treatment (5 doses). Causality assessed as not related.
- 53 year old White female (#5093) with no history of smoking experienced lobar pneumonia on Day 83 after 2 doses of the study product. Causality assessed as not related.
- 53 year old Asian female (#5227) treated with 5mg of prednisolone and multiple NSAIDS was hospitalized for acute bacterial gastroenteritis (blood cultures negative) on Day 200, 2 days after her last administration of guselkumab (5 doses). Causality assessed as probably related.

There were no reports of tuberculosis or opportunistic infections.

Two subjects in the guselkumab 50 mg group discontinued the study drug due to the following adverse events:

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- 62 year old White female (#5089) receiving methylprednisolone with a history of hypertension treated with amlodipine who developed renal insufficiency on Day 121 after 4 doses of the study product. Causality assessed as doubtful.
- 56 year old White female (#5415) receiving methylprednisolone with chronic lung disease developed an upper respiratory tract infection on Day 166 after 4 doses of the study product. Causality assessed as not related.

There was one injection site reaction in guselkumab 50 mg group (1.8%) and one in the guselkumab 200 mg group (1.9%).

Trial PSO3005:

(b) (4)

[redacted]

3) **Subgroup Analysis of Safety**

The following tables provide an analysis of selective safety findings by demographic subgroup.

Relative Risk of Serious Adverse Events (SAEs) in Weeks 0-16 by Subgroup

Safety data from Trials 3001 and 3002 was analyzed to determine the relative risk of a subject treated with guselkumab in Weeks 0-16 to experience a serious adverse event compared with a subject treated with placebo. In this analysis of selected demographic subgroups (including sex, age, race, ethnicity and region), relative risk was defined as the ratio of the probability of an

Reference ID: 4123785

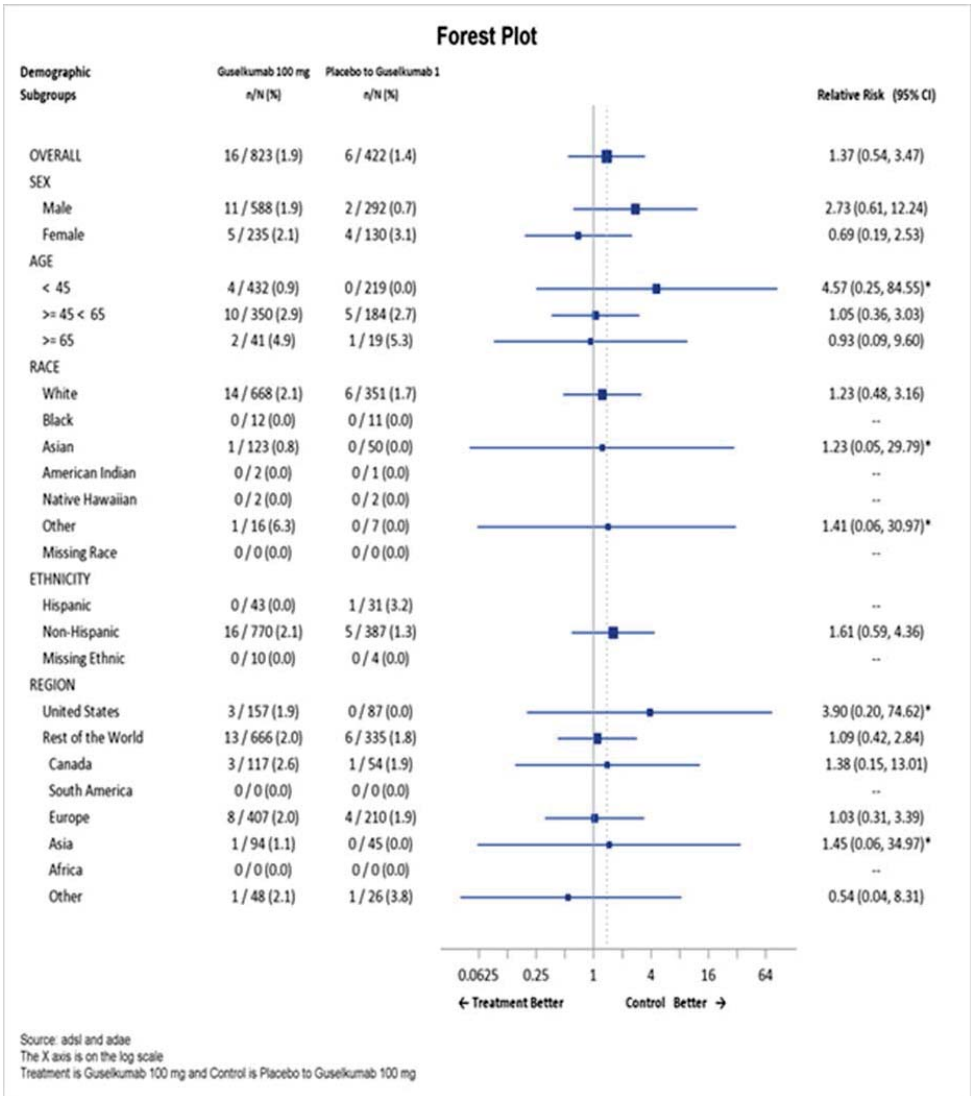
event occurring in the guselkumab group and placebo group (relative risk rate = $\frac{a}{a+b} \backslash \frac{c}{c+d}$)[18]. The results, as summarized in the following table and forest plot showed no statistically significant differences.

Table 48: Relative Risk of Serious Adverse Events (SAEs) in Weeks 0-16 by Subgroup

Subgroup	Guselkumab N=823		Placebo N=422		Relative Risk (95% CI)
	n (%)	Total,N	n (%)	Total,N	
Safety Subgroup (TRTEMFL = 'Y' and AESER = 'Y' and W16FL = 'Y')	16 (1.9)	823	6 (1.4)	422	1.37 (0.54, 3.47)
SEX					
Male	11 (1.9)	588	2 (0.7)	292	2.73 (0.61, 12.24)
Female	5 (2.1)	235	4 (3.1)	130	0.69 (0.19, 2.53)
AGE					
< 45	4 (0.9)	432	0 (0.0)	219	4.57 (0.25, 84.55)*
>= 45 < 65	10 (2.9)	350	5 (2.7)	184	1.05 (0.36, 3.03)
>= 65	2 (4.9)	41	1 (5.3)	19	0.93 (0.09, 9.60)
RACE					
White	14 (2.1)	668	6 (1.7)	351	1.23 (0.48, 3.16)
Black	0 (0.0)	12	0 (0.0)	11	--
Asian	1 (0.8)	123	0 (0.0)	50	1.23 (0.05, 29.79)*
ETHNICITY					
Hispanic	0 (0.0)	43	1 (3.2)	31	--
Non-Hispanic	16 (2.1)	770	5 (1.3)	387	1.61 (0.59, 4.36)
REGION					
United States	3 (1.9)	157	0 (0.0)	87	3.90 (0.20, 74.62)*
Rest of the World	13 (2.0)	666	6 (1.8)	335	1.09 (0.42, 2.84)
Canada	3 (2.6)	117	1 (1.9)	54	1.38 (0.15, 13.01)
Europe	8 (2.0)	407	4 (1.9)	210	1.03 (0.31, 3.39)
Asia	1 (1.1)	94	0 (0.0)	45	1.45 (0.06, 34.97)*

Source: Office of Computational Science (OCS), datasets: adsl, adae; Safety Subgroup (TRTEMFL = 'Y' and AESER = 'Y' and W16FL = 'Y')

[18] Where a=adverse event with guselkumab treatment ; c=no adverse event with guselkumab treatment; b=adverse event with placebo treatment; d=no adverse event with placebo treatment



Source: Office of Computational Science (OCS).

Relative risk of Treatment Emergent Adverse Events (TEAEs) in Weeks 0-16 by Subgroup

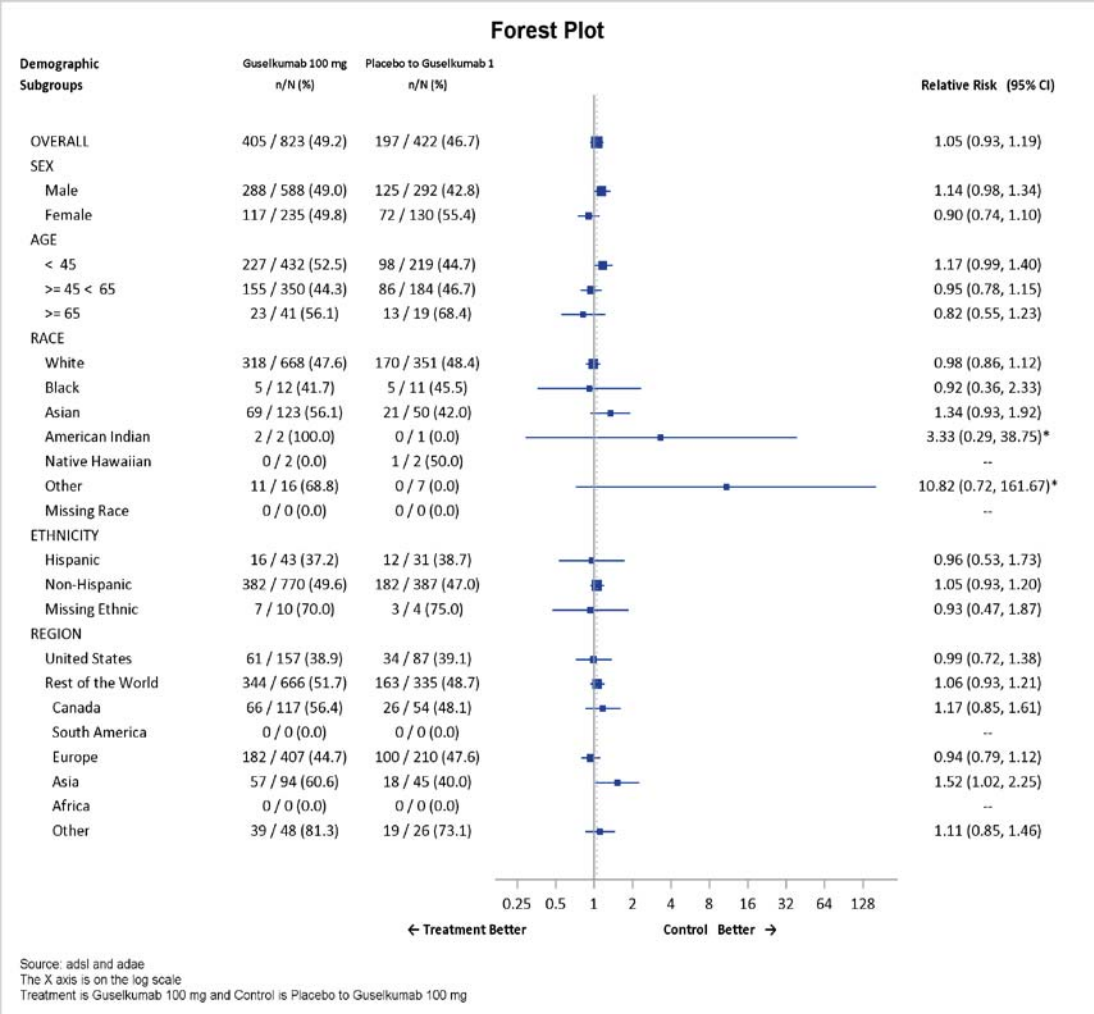
Safety data from Trials 3001 and 3002 was analyzed to determine the relative risk of a subject treated with guselkumab in Weeks 0-16 to experience a treatment emergent adverse event compared with a subject treated with placebo. In this analysis of selected demographic subgroups (including sex, age, race, ethnicity and region), relative risk was defined as the ratio of the probability of an event occurring in the guselkumab group and placebo group (relative risk rate = $\frac{a}{a+b} \backslash \frac{c}{c+d}$)[19]. The results, as summarized in the following table and forest plot, showed no statistically significant differences.

1 Where a=adverse event with guselkumab treatment ; c=no adverse event with guselkumab treatment; b=adverse event with placebo treatment; d=no adverse event with placebo treatment

Subgroup	Guselkumab N=823		Placebo N=422		Relative Risk (95% CI)
	n (%)	Total, N	n (%)	Total, N	
Safety Subgroup (TRTEMFL = 'Y' and W16FL = 'Y')	405 (49.2)	823	197 (46.7)	422	1.05 (0.93, 1.19)
SEX					
Male	288 (49.0)	588	125 (42.8)	292	1.14 (0.98, 1.34)
Female	117 (49.8)	235	72 (55.4)	130	0.90 (0.74, 1.10)
AGE					
< 45	227 (52.5)	432	98 (44.7)	219	1.17 (0.99, 1.40)
>= 45 < 65	155 (44.3)	350	86 (46.7)	184	0.95 (0.78, 1.15)
>= 65	23 (56.1)	41	13 (68.4)	19	0.82 (0.55, 1.23)
RACE					
White	318 (47.6)	668	170 (48.4)	351	0.98 (0.86, 1.12)
African American	5 (41.7)	12	5 (45.5)	11	0.92 (0.36, 2.33)
Asian	69 (56.1)	123	21 (42.0)	50	1.34 (0.93, 1.92)
ETHNICITY					
Hispanic	16 (37.2)	43	12 (38.7)	31	0.96 (0.53, 1.73)
Non-Hispanic	382 (49.6)	770	182 (47.0)	387	1.05 (0.93, 1.20)
REGION					
United States	61 (38.9)	157	34 (39.1)	87	0.99 (0.72, 1.38)
Rest of the World	344 (51.7)	666	163 (48.7)	335	1.06 (0.93, 1.21)
Canada	66 (56.4)	117	26 (48.1)	54	1.17 (0.85, 1.61)
Europe	182 (44.7)	407	100 (47.6)	210	0.94 (0.79, 1.12)
Asia	57 (60.6)	94	18 (40.0)	45	1.52 (1.02, 2.25)

Source: Office of Computational Science (OCS), datasets: adsl, adae; Safety Subgroup (TRTEMFL = 'Y' and AESER = 'Y' and W16FL = 'Y')

Reference ID: 4123785



Source: Office of Computational Science (OCS),

Analyses of Selected Adverse Reactions by Demographic Subgroup

Upper Respiratory Infections

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	82/588 (13.9)	14/131 (10.7)	32/292 (11.0)
Females	36/235 (15.3)	7/65 (10.8)	22/130 (16.9)
Age			
18-64	112/782 (14.3)	19/176 (10.8)	50/403 (12.4)
65+	6/41 (14.6)	2/20 (10.0)	4/19 (21.1)
Race			
White	98/668 (14.7)	20/162 (12.3)	51/351 (14.5)
Black	1/12 (8.3)	1/11 (9.1)	1/11 (9.1)
Asian	15/123 (12.2)	0/16 (0)	2/50 (4.0)
Other	4/20 (20.0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	62/465 (13.3)	5/99 (5.1)	30/252 (11.9)
> 90 kg	56/358 (15.6)	16/96 (16.7)	24/170 (14.1)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

Headache

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	21/588 (3.6)	2/131 (1.5)	7/292 (2.4)
Females	17/235 (7.2)	0/65 (0)	7/130 (5.4)
Age			
18-64	37/782 (4.7)	2/176 (1.1)	13/403 (3.2)
65+	1/41 (2.4)	0/20 (0)	1/19 (5.3)
Race			
White	34/668 (5.1)	2/162 (1.2)	13/351 (3.7)
Black	0/12 (0)	0/11 (0)	0/11 (0)
Asian	3/123 (2.4)	0/16 (0)	1/50 (2.0)
Other	1/20 (5.0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	21/465 (4.5)	1/99 (1.0)	8/252 (3.2)
> 90 kg	17/358 (4.7)	1/96 (1.0)	6/170 (3.5)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

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Injection Site Reactions

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	25/588 (4.3)	8/131 (6.1)	6/292 (2.1)
Females	12/235 (5.1)	7/65 (10.8)	6/130 (4.6)
Age			
18-64	37/782 (4.7)	14/176 (8.0)	10/403 (2.5)
65+	0/41 (0)	1/20 (5.0)	2/19 (10.5)
Race			
White	28/668 (4.2)	11/162 (6.8)	8/351 (2.3)
Black	0/12 (0)	1/11 (9.1)	1/11 (9.1)
Asian	8/123 (6.5)	2/16 (12.5)	3/50 (6.0)
Other	1/20 (5.0)	1/7 (14.3)	0/10 (0)
Baseline Weight			
≤ 90 kg	21/465 (4.5)	9/99 (9.1)	8/252 (3.2)
> 90 kg	16/358 (4.5)	5/96 (5.2)	4/170 (2.4)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

Arthralgia

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	15/588 (2.6)	3/131 (2.3)	4/292 (1.4)
Females	7/235 (3.0)	1/65 (1.5)	5/130 (3.8)
Age			
18-64	21/782 (2.7)	4/176 (2.3)	9/403 (2.2)
65+	1/41 (2.4)	0/20 (0)	0/19 (0)
Race			
White	17/668 (2.5)	4/162 (2.5)	8/351 (2.3)
Black	0/12 (0)	0/11 (0)	1/11 (9.1)
Asian	5/123 (4.1)	0/16 (0)	0/50 (0)
Other	0/20 (0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	15/465 (3.2)	2/99 (2.0)	6/252 (2.4)
> 90 kg	7/358 (2.0)	2/96 (2.1)	3/170 (1.8)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

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Elevated Liver Enzymes

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	15/588 (2.6)	4/131 (3.1)	6/292 (2.1)
Females	6/235 (2.6)	0/65 (0)	2/130 (1.5)
Age			
18-64	19/782 (2.4)	4/176 (2.3)	7/403 (1.7)
65+	2/41 (4.9)	0/41 (0)	1/19 (5.3)
Race			
White	17/668 (2.5)	3/162 (1.9)	7/351 (2.0)
Black	1/12 (8.3)	0/11 (0)	0/11 (0)
Asian	3/123 (2.4)	1/16 (6.3)	1/50 (2.0)
Other	0/20 (0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	9/465 (1.9)	2/99 (2.0)	4/252 (1.6)
> 90 kg	12/358 (3.4)	2/96 (2.1)	4/170 (2.4)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

Diarrhea

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	9/588 (1.5)	2/131 (1.5)	2/292 (0.7)
Females	4/235 (1.7)	1/65 (1.5)	2/130 (1.5)
Age			
18-64	13/782 (1.7)	3/176 (1.7)	4/403 (1.0)
65+	0/41 (0)	0/20 (0)	0/19 (0)
Race			
White	10/668 (1.5)	1/162 (0.6)	4/351 (1.1)
Black	0/12 (0)	1/11 (9.1)	0/11 (0)
Asian	3/123 (2.4)	0/16 (0)	0/50 (0)
Other	0/20 (0)	1/7 (14.3)	0/10 (0)
Baseline Weight			
≤ 90 kg	8/465 (1.7)	0/99 (0)	1/252 (0.4)
> 90 kg	5/358 (1.4)	3/96 (3.1)	3/170 (1.8)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

Reference ID: 4123785

Gastroenteritis

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	5/588 (0.9)	3/131 (2.3)	2/292 (0.7)
Females	6/235 (2.6)	1/65 (1.5)	2/130 (1.5)
Age			
18-64	11/782 (1.4)	4/176 (2.3)	4/403 (1.0)
65+	0/41 (0)	0/20 (0)	0/19 (0)
Race			
White	10/668 (1.5)	4/162 (2.5)	2/351 (0.6)
Black	0/12 (0)	0/11 (0)	0/11 (0)
Asian	1/123 (0.8)	0/16 (0)	2/50 (4.0)
Other	0/20 (0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	8/465 (1.7)	2/99 (2.0)	2/252 (0.8)
> 90 kg	3/358 (0.8)	2/96 (2.1)	2/170 (1.2)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

Tinea Infections

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	7/588 (1.2)	0/131 (0)	0/292 (0)
Females	2/235 (0.9)	0/65 (0)	0/130 (0)
Age			
18-64	9/782 (1.2)	0/176 (0)	0/403 (0)
65+	0/41 (0)	0/20 (0)	0/19 (0)
Race			
White	4/668 (0.6)	0/162 (0)	0/351 (0)
Black	0/12 (0)	0/11 (0)	0/11 (0)
Asian	4/123 (3.3)	0/16 (0)	0/50 (0)
Other	1/20 (5.0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	5/465 (1.1)	0/99 (0)	0/252 (0)
> 90 kg	4/358 (1.1)	0/96 (0)	0/170 (0)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

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Herpes Simplex Infections

Subgroups	Guselkumab (N=823) m/n* (%)	Adalimumab (N=196) m/n* (%)	Placebo (N=422) m/n* (%)
Gender			
Males	5/588 (0.9)	0/131 (0)	0/292 (0)
Females	4/235 (1.7)	0/65 (0)	2/130 (1.7)
Age			
18-64	9/782 (1.2)	0/176 (0)	1/403 (0.2)
65+	0/41 (0)	0/20 (0)	1/19 (5.3)
Race			
White	7/668 (1.0)	0/162 (0)	1/351 (1.0)
Black	0/12 (0)	0/11 (0)	0/11 (0)
Asian	2/123 (1.6)	0/16 (0)	1/50 (2.0)
Other	0/20 (0)	0/7 (0)	0/10 (0)
Baseline Weight			
≤ 90 kg	7/465 (0.8)	0/99 (0)	2/252 (0.8)
> 90 kg	2/358 (0.6)	0/96 (0)	0/170 (0)

*m/n = number of participants with adverse reaction (m) in the subgroup (n)
Source: Statistical Review's Tables

13.4. Clinical Pharmacology Appendices

13.4.1. Summary of Bioanalytical Method Validation and Performance

13.4.1.1. PK assay: Methods for determination of guselkumab levels in human serum

The Applicant used two validated bioanalytical methods to determine serum guselkumab concentrations during clinical development, namely a dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) method and an electrochemiluminescence immunoassay (ECLIA) assay using the Meso Scale Discovery (MSD®) platform. The initial Phase 1 and Phase 2 studies used the DELFIA method whereas the phase 3 studies used ECLIA assay (Table 49). The label proposed by the Applicant includes data generated by both methods. The Applicant conducted a cross-validation study (validation report CP2014V-027-A1) which demonstrated that the DELFIA method and the ECLIA method are comparable.

Table 49: Summary of assay(s) used for quantification of guselkumab in serum in the clinical development program for psoriasis

	Study #	Assay	Validation reports
Phase 1	PSO1001 PSO1002 NAP1001	DELFIA	CP2009V-056, Addendums A1:A7
	NAP1002	ECLIA	CP2014V-027 Addendums A1:A5
Phase 2	PSO2001	Original analysis: DELFIA Re-analysis*: ECLIA	CP2009V-056, Addendums A1:A7 CP2014V-027 Addendums A1:A5
Phase 3	PSO3001 PSO3002 PSO3003	ECLIA ECLIA ECLIA	CP2014V-027 Addendums A1:A5

* Samples were re-analyzed with the ECLIA platform to allow for data from this study to be pooled with Phase 3 studies for the population PK and PK/PD modeling.
Data source: Reviewer generated table based on Table 2 from summary of clinical pharmacology

Assay description and procedure

DELFIA: The assay is a solid-phase sandwich immunoassay that utilizes dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) technology from PerkinEimer Inc. The assay uses CNTO2254 (C1644A, a mouse monoclonal antibody specific for the variable region of guselkumab) coated on microtiter plates, that serves as the binding surface for the assay. Following a blocking step, the guselkumab in the sample is bound to the CNTO2254 coated onto the plates. Biotinylated-CNTO5203 (C1642A, a mouse monoclonal antibody specific for the variable region of guselkumab), is then added and binds to guselkumab. Streptavidin-Europium binds to the immobilized complex on the plate and an enhancement solution is added to facilitate signal generation. The amount of fluorescence emitted is proportional to the concentration of guselkumab in the sample.
ECLIA: The assay is a solid-phase electrochemiluminescence-based immunoassay (ECLIA) format on the MSD® platform. Streptavidin-coated 96-well plates serve as the support surface for the assay. The assay plate is blocked for at least 15 minutes with Assay Buffer. The

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biotinylated-CNTO2254 (C1644A) solution is used as the capture antibody. Following incubation, the plate is washed. Next, the SulfoTag-CNTO5203 (C1642A) solution is added to the assay plate. Following incubation, the plate is washed and read buffer substrate is added and the electrochemiluminescent signal is read on the MSD ® Sector Imager 6000 reader.
The validation parameters of both these assays are summarized in Table 50.

Table 50: Summary of method validation parameters for DELFIA and ECLIA assays for measurement of guselkumab in human serum

Assay Method	DEFLIA	ECLIA
Minimum Required Dilution (MRD)	1:10	1:10
Standard curve fit	5-Parameter logistic (auto estimate) regression with I/F2 weighting	Wagner (log-log Quadratic) regression with no weighting
Standard Curve range (LLOQ to ULOQ)	4.00 ng/mL to 128.00 ng/mL	1.00 ng/mL to 64.00 ng/mL
Lowest Quantifiable Sample Concentration of the Assay (LLOQ x MRD)	40.00 ng/mL	10.00 ng/mL
Accuracy (% Bias)	ULOQ +0.63 High -10.44 Mid -17.44 Low -19.00 LLOQ -12.75	ULOQ +1.38 High +0.77 Mid -0.75 Low -1.33 LLOQ -1.00
Intra-Assay Precision (%CV)	ULOQ 3.32 High 0.86 Mid 2.11 Low 1.80 LLOQ 1.97	ULOQ 2.62 High 5.33 Mid 2.79 Low 3.60 LLOQ 7.20
Inter-assay Precision (%CV)	ULOQ 3.93 High 1.75 Mid 3.50 Low 2.31 LLOQ 1.97	ULOQ 3.92 High 6.58 Mid 5.21 Low 4.70 LLOQ 7.81
Hook Effect	No hook effect was observed.	No hook effect was observed.
Dilution linearity	Linear from 1:10 to 1:156,250	Linear from 1:10 to 1:5000

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Specificity	No cross-reactivity demonstrated with IL-23 at a 50-fold molar excess to LLOQ guselkumab concentration	Presence of IL-23 affects the estimation of guselkumab at molar ratios greater than 1:1 (tested at 10.00 ng/mL). Presence of non-neutralizing anti-drug antibodies (200 and 500 ng/mL) affected recovery of guselkumab at LLOQ (1 ng/mL) but didn't affect recovery at concentrations of 8 ng/mL.
Freeze thaw stability	8 freeze/thaw cycles	8 freeze/thaw cycles
Bench-Top Stability	24 hours at room temperature 4 weeks at 4°C	24 hours at room temperature 4 weeks at 4°C
Long Term Storage Stability	4 weeks at 4°C 8 weeks at -20°C 4 years at -70°C 4 weeks as stored standards at -70°C	4 weeks at 4°C 4 weeks at -20°C 4 years at -70°C 1 week for standard curve calibrator at 4°C
Incurred Sample Reanalysis	Method reproducibility was demonstrated using 28 samples from CNT01959PS01001 • 27 / 28 showed reanalyzed values within acceptable limits).	Method reproducibility was evaluated using samples from CNTO1959PPP2001 and CNT01959PS03003. • Three out of four sets of ISRs from study PPP2001 failed. • The final run conducted using manual pipetting passed. • The Applicant didn't provide a cause for the failed ISR runs. • However, the additional ISR using the samples from study PSO3003 was acceptable (40 / 40 showed reanalyzed values within acceptable limits).

Source: Applicant's validation report CP2009V-056 along with addendums A1:A7 and CP2014V-027 along with addendums A1:A5

Method cross-validation: DELFIA vs. ECLIA

The Applicant conducted a cross-validation study (validation report CP2014V-027-A1) which demonstrated that the DELFIA method and the ECLIA method are comparable. The study compared the performance characteristics of the ECLIA method with the DELFIA method using 30 quality control (QC) samples and 30 incurred study samples as a part of the cross-validation study. A total of 28 out of 30 control samples were within acceptance criteria (≤30%) for percent difference in concentration. Also, a total of 23 out of 28 incurred study samples analyzed by both methods produced results that were ≤30% for percent difference in concentration. Based on the results from the cross-validation study, the methods used for the quantification of guselkumab in human serum by ECLIA and DELFIA can be considered comparable.

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13.4.1.2. Assay for serum PD markers

The applicant performed exploratory analysis of serum-based biomarkers believed to be associated with the mechanism of action of guselkumab. IL-17A, IL-17F, IL-22 and IL-23, as well as 3 additional inflammatory markers associated with psoriasis CCL22/MDC (macrophage derived chemokine), CXCL4/MIP-1β (macrophage inflammatory protein beta) and CXCL/IL-8 (IL-8) were analyzed in a subset of subjects.

Assay description and procedure – for multiple PD markers
These serum proteins were analyzed using antibody-based assays as summarized in Table 51 .

Table 51: Details of assays used for analysis of serum PD

Analytes	LLOQ (pg/mL)	ULOQ (pg/mL)	Assay details
MDC	10.3	10600	Meso Scale Discovery #K151AOH-2, Lot# 195308 V-PLEX Chemokine Panel 1 (human) Kit
MIP-1b	0.98	1010	
IL-8	0.14	575	Meso Scale Discovery #K151AOH-2, Lot# 195302 V-PLEX Proinflammatory Panel 1 (human) Kit
IL-17A	0.034	20	Singulex #03-0103-00 Human IL-17A (V2) Immunoassay, Lot# 2778079
IL-17F	0.39	100	Singulex #03-0102-00 Human IL-17F (V2) Immunoassay, Lot# 2778080
IL-22	0.24	250	Singulex plate-based assay (developed in-house)
IL-23	0.1	100	Singulex #03-0112-00 Human IL-23 Immunoassay, Lot# 2792547

Data source: Immunology Biomarker Exploratory Report CNTO1959PSO3001

Reviewer comment: The applicant has claimed that the analysis of serum PD marker were conducted using validated platforms (Singulex high-sensitivity and MSD immunoassay). However, the applicant hasn't provided a validation memo for these methods with this BLA for our review. Based on the limited method details provided in the BLA, these assays cannot be considered validated and as such the results from these assays should be considered exploratory.

13.4.1.3. Assay for assessment of immunogenicity

The applicant used validated assays to assess the immunogenicity of guselkumab in human serum. Samples were first tested in an electrochemiluminescence (ECL)-based immunoassay (ECLIA) for the detection of antibodies capable of binding to guselkumab (i.e., ADA assay). Samples confirmed to be positive for binding antibodies were subsequently tested in a competitive ligand binding assay to detect neutralizing anti-guselkumab antibodies (NAb). Refer to CMC section for review of the assays by OBP immunogenicity reviewer (Section 4 of multi-disciplinary review).

Below is a summary of immunogenicity assay information relevant to clinical pharmacology assessments.

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Immunogenicity assay sensitivity and drug tolerance
Table 52 provides summary of the assay sensitivity and drug tolerance levels for these assays. The ADA assay and the NAb assay have a drug tolerance of 3.125 ug/mL for detecting 5 ng/mL of ADA positive control and 0.83 ug/mL for detecting 500 ng/mL of NAb positive control, respectively. In the Phase 3 studies, trough serum guselkumab levels were above the drug tolerance level for the ADA assay in approx. 14 % of the subjects. The drug tolerance level for the ADA assay covers the trough serum guselkumab levels observed in majority of the subjects in the Phase 3 studies and the assay is capable of detecting up to 5 ng/mL of ADA positive control; therefore, the ADA assay may be considered adequate for assessment of ADA incidence. Refer to the Product Quality Review for more detailed information regarding the details of the immunogenicity assays.

Table 52: Sensitivity and drug tolerance of the immunogenicity assays for detecting binding (ADA) and neutralizing anti-drug antibodies (NAb) against guselkumab in Phase 2 and Phase 3 studies

Immunogenicity Assays	Validation Report	Sensitivity	Drug tolerance
ADA Assay	CP2010V-008	3.1 ng/mL (monoclonal control)	3125 ng/mL (using 15 ng/mL of control ADA)
NAb assay	CP2013V-057, CP2013V-057-A2	157.53 ng/mL (polyclonal control)	834.56 ng/mL (using 500 ng/mL of the polyclonal NAb control)

Source: Applicant's validation reports CP2010V-008, CP2013V-057, CP2013V-057-A2

Binding Anti-drug Antibody (ADA) Assay:
The assay scheme consists of screening, titration, and specificity test methods. The screening test method is used to detect potentially positive anti-drug antibodies (ADA) to guselkumab in human serum samples. A titration method is used to provide a quasi-quantitative estimate of ADA level in human serum. The specificity test method is used to determine if potentially ADA positive samples are specific to guselkumab. In addition, a blocking antibody to IL-23 was used to determine if potentially positive reactivity to guselkumab is due to serum IL-23 instead of ADA.
This ADA assay is based on electrochemiluminescence (ECL) bridging immunoassay using the Meso Scale Discovery (MSD) platform. In this assay, the sample is incubated simultaneously with biotin- CNTO1959 and ruthenium-CNTO1959. A bridge is formed when the positive control or any ADA present in the sample binds to both Biotin-guselkumab and Ru-guselkumab, forming a complex. The biotin-CNTO1959 in the complex is captured on a streptavidin coated plate, unbound proteins are washed away, and signal is detected when the ruthenium-guselkumab reagent, simultaneously captured on the plate through a molecular bridge via the ADA, is stimulated to luminesce. The amount of ECL signal is proportional to the amount of anti-guselkumab antibodies in the sample.

Neutralizing Antibody (NAb) Assay:
For the detection of neutralizing antibodies, the Applicant developed an electrochemiluminescence-based competitive ligand binding assay using the MSD platform to detect anti-guselkumab NAbs in human serum samples. This method utilizes biotin labeled guselkumab as the capture reagent, and ruthenium-labeled hIL-23 as the detection reagent. Serum samples are pre-treated with acetic acid to dissociate drug/ADA complexes, then treated with biotin- hIL-23 after pH neutralization to remove exogenous drug. Samples are subsequently

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incubated with an unconjugated anti-hIL-23 monoclonal antibody, CNTO 856, to block free hIL-23. Subsequently, the pre-treated samples are incubated with biotin-guselkumab to allow the binding of NAbs to biotin-guselkumab. The assay mixture is then added to a streptavidin-coated MSD assay plate, enabling the capture of biotin-CNTO 1959 on the carbon electrode surface. After removal of unbound proteins by washing, the captured biotin-CNTO 1959 is detected by Ruthenium-hIL-23, emitting an ECL signal. NAbs binding to biotin-guselkumab during the pre-incubation competitively prevents it from binding to Ruthenium-hIL-23, thus, reducing the assay signal. Therefore, the level of NAb activity is inversely proportional to the measured assay signal.

13.4.2. Biopharmaceutics: Comparative PK Study

The drug substance (DS) and drug products (DP) used during the clinical development of guselkumab for the psoriasis indication are listed in Table 53.

Drug substance:
There were 2 versions of the DS manufacturing process that were designated according to the associated development phases. (b) (4)

- Phase 1/2 Process – associated with toxicology studies, Phase 1 studies, and Phase 2 study; manufactured at Janssen R&D, Spring House, PA, USA.
- Phase 3 Process – associated with toxicology studies and Phase 3 studies; manufactured, at Biogen Inc (BIIB), Research Triangle Park, NC, USA, and Janssen Biologics (Ireland), Cork, Ireland (JBIL).

Table 53: Summary of drug substance and drug products evaluated in the guselkumab clinical development program

	Study #	Drug substance	Formulation	Presentation
Phase 1	PSO1001	Ph 1/2 Process	Lyophilized	LYO
	PSO1002	Ph 1/2 Process	Lyophilized	LYO
	NAP1001	Ph 1/2 Process (LYO) Ph 3 process (PFS (b) (4) and PFS (b) (4))	Lyophilized Liquid Liquid	LYO PFS (b) (4) PFS (b) (4)
	NAP1002	Ph 3 Process	Liquid	PFS (b) (4)
Phase 2	PSO2001	Ph 1/2 Process	Lyophilized	(b) (4)
Phase 3	PSO3001	Ph 3 Process	Liquid	PFS (b) (4)
	PSO3002	Ph 3 Process	Liquid	PFS (b) (4)
	PSO3003	Ph 3 Process	Liquid	PFS (b) (4)

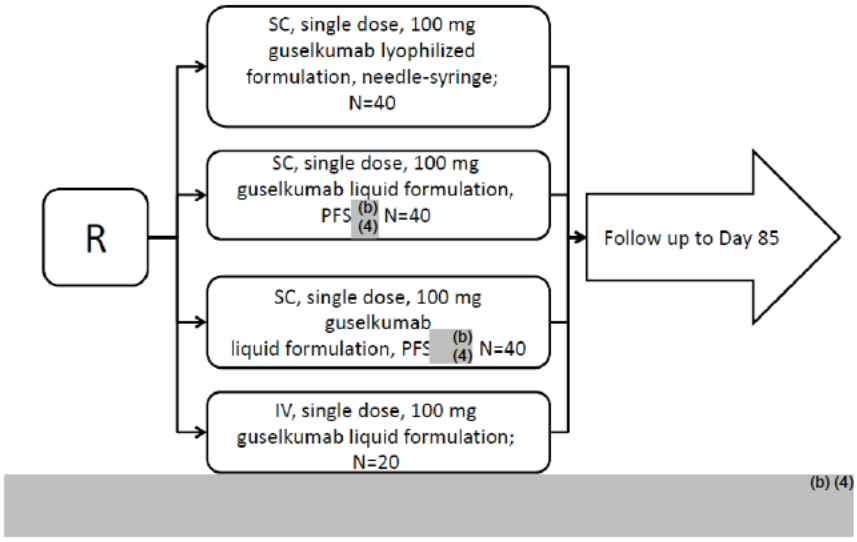
Drug product:
The intended commercial presentation is the liquid formulation in PFS (b) (4) (prefilled syringe with (b) (4) Passive Needle Guard). It is supplied as a single-use sterile solution in a 1

mL glass syringe with a 27-gauge, ½-inch fixed needle and a (b) (4) rigid needle shield. The formulation is composed of 100 mg/mL guselkumab, containing L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection at pH 5.8. The intended commercial product is the same as the product utilized in the Phase 3 studies. Three different guselkumab formulations/presentations, including liquid-in-vial (lyophilized formulation, FLP), PFS (b) (4) and PFS (b) (4) device) were evaluated and two were used in psoriasis Phase 2 and Phase 3 trials evaluating efficacy and safety of guselkumab (Table 53).

Prior to the start of Phase 3 program, the Applicant conducted a PK comparability study with all three presentations (LYO, PFS (b) (4) and PFS (b) (4) following a single SC dose of 100 mg in healthy subjects (Study NAP1001). Results supported PK comparability between LYO and PFS (b) (4) but PFS (b) (4) did not achieve similar PK as LYO or PFS (b) (4) Further details of the study are described below.

PK comparability study
Study NAP1001 was a Phase 1, open-label, randomized, parallel study in healthy subjects (Table 54). We note that this study wasn't powered to establish bioequivalence. Details of the study design are summarized in Figure 23.

Figure 23: Study scheme for NAP1001



Source: Figure 1 from study protocol for CNTO1959NAP1001)

Table 54: Summary of study details for PK comparability study CNTO1959NAP1001

Products compared	• Lyophilized Formulation (LYO) • Liquid formulation in a prefilled syringe (b) (4) • Liquid formulation in a prefilled syringe (b) (4)
Study design	Open-label, Randomized, Parallel Study
Study population	Healthy men or women (18-65 yo)
# of subjects randomized and completed the study	141 were randomized and treated in the study. NOTE: 6 subjects discontinued the study

# of subjects considered for PK comparability	• 40 subjects in the SC LYO group (39 for AUC_{0-70d}) • 40 subjects in the SC PFS(b) (4) group (35 for AUC_{0-70d}) • 41 subjects in the SC PFS (b) (4) group (40 for AUC_{0-70d})
Criteria for exclusion	Insufficient sampling time points or poorly characterized terminal elimination phase (defined as adjusted $R^2 < 0.80$)
Guselkumab dose	100 mg SC and 100 mg IV
Administration route	SC and IV
Primary endpoints	C_{max} and AUC_{0-70d}
PK sampling timepoints	Day 1 (pre-dose), 2, 3, 4, 6, 8, 11, 15, 18, 22, 29, 36, 43, 57, 85.

Results from (Table 55) this study indicated that the systemic exposure (C_{max} and AUC_{0-70d}) of guselkumab was comparable between the Phase 3 liquid formulation (PFS (b) (4)) and the Phase 2 lyophilized formulation (LYO). The Applicant used the statistical method for bioequivalence testing to assess PK comparability even though the study was not powered to meet the bioequivalence criteria. The geometric mean ratios of Cmax and AUC_{0-70d} were around 1 with 90% confidence interval being within the range of 0.80-1.25 (see table 4.2.3 below). Furthermore, this study also supported the Phase 3 study dose selection based on data from the Phase 2 dose-finding study which used the lyophilized formulation.

Additionally, the mean absolute bioavailability (F) of guselkumab following a single 100 mg SC administration was 47.6% and 48.7%, for lyophilized formulation and liquid formulation in PFS-(b) (4) respectively.

Table 55: Comparison of guselkumab exposure parameters following a single SC dose of 100 mg from LYO, PFS(b) (4) and PFS (b) (4) presentations

Parameter	PFS (b) (4)/LYO		PFS (b) (4)/LYO		PFS (b) (4)/ PFS (b) (4)	
	GMR	90 % CI	GMR	90 % CI	GMR	90 % CI
AUC_{inf}*	0.97	0.83 - 1.13	1.16	0.99 - 1.35	1.20	1.03 - 1.40
AUC_{0-70d}	0.97	0.83 - 1.12	1.15	0.99 - 1.34	1.20	1.03 - 1.40
Cmax (µg/mL)	0.99	0.86 - 1.13	1.16	1.01 - 1.33	1.18	1.03 - 1.35

*Number of subjects with available AUC_{0-inf} was 39, 35, and 40 for LYO, PFS (b) (4) PFS (b) (4)

Further, the results also suggested that using the same liquid formation of guselkumab, the SC delivery by the PFS (b) (4) device didn't meet the BE criterion when compared to PFS (b) (4). The geometric mean ratios of Cmax and AUC_{0-70d}, from PFS (b) (4) to PFS (b) (4) were 1.18 to 1.20 with upper bound of 90% CI for both Cmax and AUC exceeding 1.25. However, the Applicant is not pursuing the PFS (b) (4) presentation.

Table 56: List of subjects excluded from the statistical analysis for assessing comparability of three formulation/presentations.

Treatment Group	Subject ID	PK Parameters Excluded	Reason for Exclusion
SC lyophilized formulation	1002-102030	AUC_{last}, AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	Missing 3 consecutive samples
SC liquid formulation PFS (b) (4)	1003-103006	AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	$R^2 < 0.80$
	1003-103013	AUC_{last}, AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	Insufficient blood sampling (last sample collected on Day 22)
	1003-103044	AUC_{last}, AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	Insufficient blood sampling (last sample collected on Day 29)
	1003-103068	AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	$R^2 < 0.80$
	1003-103091	AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	$R^2 < 0.80$
SC liquid formulation PFS (b) (4)	1003-103033	AUC_{last}, AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F, and F	Insufficient blood sampling (last sample collected on Day 7)
IV liquid formulation	1003-103038	AUC_{0-70d}, AUC_{inf}, $T_{1/2}$, CL, and V_z	$R^2 < 0.80$

Data source: Table 5 Clinical study report CNTO1959NAP1001

Reviewer comments:
Verification of the Applicant's PK comparability analysis was done by the review team using a internal Agency software and the Applicant's analysis was confirmed.
The Applicant excluded 7 subjects from the statistical analysis assessing the comparability of the three formulations/presentations. Table 56 lists the excluded subjects along with Applicant's rationale for the exclusion of each of these subjects. A sensitivity analysis was conducted by the review team by including the data from these subjects in the PK comparison.
Including the five subjects from the PFS (b) (4) group along with the one subject from the LYO group in the analysis didn't affect the outcome of the PK comparison between the lyophilized formulation and liquid formulation in PFS (b) (4) The geometric mean ratios of Cmax and AUC_{0-70d}, from PFS (b) (4) to LYO were close to 1 with 90% confidence interval being within the range of 0.80-1.25 confirming that the exposures from the lyophilized formulation and liquid formulation in PFS (b) (4) were comparable.

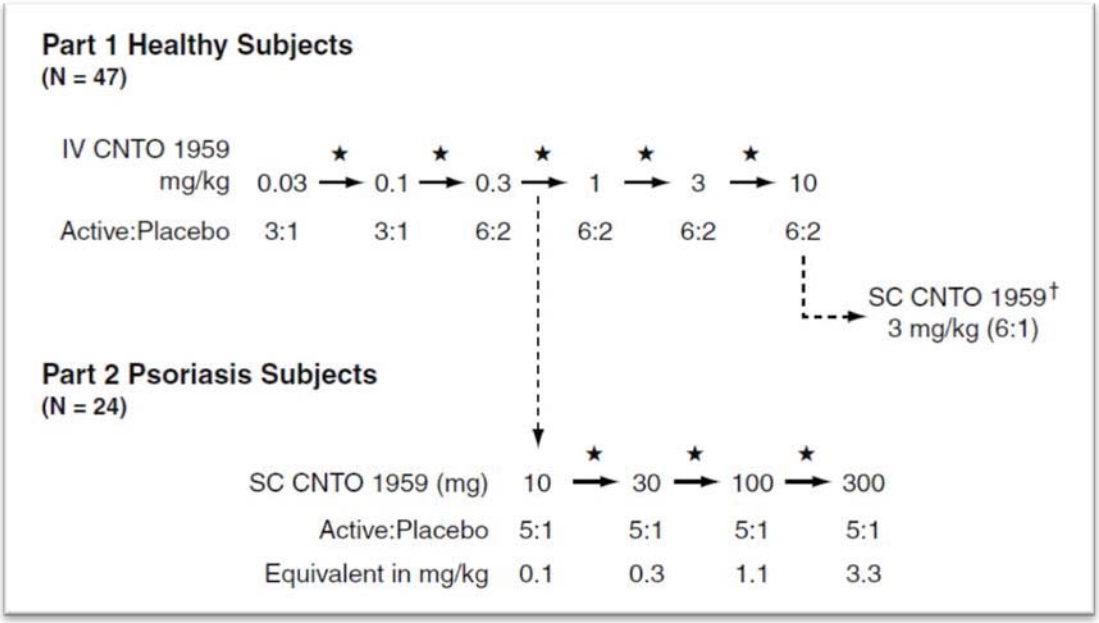
Similarly the sensitivity analysis indicated that inclusion of the data from the one subject from the PFS (b) (4) group and one subject from the LYO group didn't affect the outcome of the PK comparison between the lyophilized formulation and liquid formulation in PFS (b) (4) The geometric mean ratios of Cmax and AUC_{0-70d}, from PFS (b) (4) to LYO were greater than 1 with upper bound of 90% CI for both Cmax and AUC exceeding 1.25 confirming the Applicant's conclusion that exposures from the liquid formulation in PFS (b) (4) was higher than lyophilized formulation.

13.4.3. Pharmacokinetics: Individual Study Reports

CNTO1959PSO1001 (Single-dose PK study in healthy subjects and Psoriasis subjects)

Study PSO1001 was a randomized, double-blind, placebo-controlled, ascending dose study in healthy subjects and subjects with psoriasis. The study was conducted in 2 parts (Figure 24)
Part 1 of PSO1001 consisted of Part 1 IV and Part 1 SC, which involved administration of guselkumab IV and SC, respectively, to healthy subjects. In Part 1 IV, ascending single doses of guselkumab or placebo (0.03, 0.1, 0.3, 1, 3, and 10 mg/kg) were administered as a single 30-minute IV infusion to sequential cohorts of healthy subjects. Subjects were randomized at a ratio of 3 active to 1 placebo at dose levels of 0.03 and 0.1 mg/kg and at a ratio of 6 active to 2 placebo at dose levels of 0.3, 1, 3, and 10 mg/kg (n=6). In part 1 SC, healthy subjects were randomly assigned to a single SC dose of 3 mg/kg (n=6) of guselkumab or placebo.
Part 2 involved SC administration of guselkumab to subjects with moderate to severe psoriasis randomized at a ratio of 5 active to 1 placebo to receive SC doses of guselkumab (10, 30, 100, and 300 mg; 5 subjects per treatment group) or placebo SC (4 subjects in total, or 1 subject per treatment group).

Figure 24: Study scheme for PSO1001

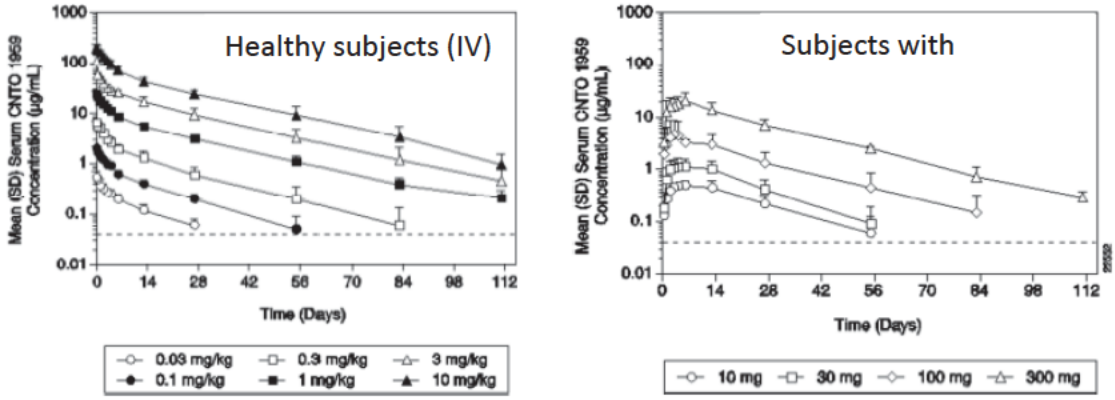


(Source: Figure 1 from study protocol for CNTO1959PSO1001)

Following a single IV administration of 0.03, 0.1, 0.3, 1, 3 or 10 mg/kg guselkumab, mean Cmax and AUC values increased in an approximately dose-proportional manner. Figure 26 provides the concentration-time profiles of guselkumab in healthy subjects and subjects with psoriasis. PK parameters estimated by non-compartment analysis are listed in Table 57 and Table 58.

Reference ID: 4123785

Figure 25: Mean (SD) Serum guselkumab concentration vs. time profiles following single IV administrations of guselkumab to healthy subjects (left panel) and following single SC administration in subjects with psoriasis (right panel)



Source: Figure 4 and Figure 5 from clinical study report PSO1001

Table 57: Summary of guselkumab pharmacokinetic parameters following single IV and SC administrations of guselkumab to healthy subjects.

	Guselkumab						
	0.03 mg/kg IV	0.1 mg/kg IV	0.3 mg/kg IV	1 mg/kg IV	3 mg/kg IV	10 mg/kg IV	3 mg/kg SC
Subjects PK evaluable	3	3	6	6	6	6	6
C_{max} (µg/mL)							
N	3	3	6	6	5	6	6
Mean (SD)	0.54 (0.157)	2.02 (0.200)	6.54 (0.739)	24.66 (3.193)	58.55 (5.278)	197.46 (33.597)	9.46 (2.498)
Median	0.47	2.07	6.55	23.85	58.59	200.36	8.46
AUC_{inf} (µg•day/mL)							
N	3	3	6	6	6	6	6
Mean (SD)	5.22 (1.422)	18.64 (3.940)	59.99 (20.643)	278.51 (28.322)	787.92 (203.050)	2214.52 (345.267)	256.99 (48.156)
Median	4.93	17.76	55.93	280.00	740.73	2261.80	251.55
$T_{1/2}$ (day)							
N	3	3	6	6	6	6	6
Mean (SD)	12.25 (0.997)	15.02 (3.155)	15.56 (5.036)	19.12 (2.151)	18.12 (3.843)	18.91 (3.885)	16.81 (2.855)
Median	12.52	16.13	14.11	19.16	17.22	19.51	16.44
CL or CL/F (mL/day/kg)[a,b]							
N	3	3	6	6	6	6	6
Mean (SD)	6.03 (1.571)	5.52 (1.109)	5.54 (2.113)	3.62 (0.376)	4.03 (1.057)	4.61 (0.729)	12.05 (2.506)
Median	6.10	5.63	5.39	3.58	4.06	4.43	11.93
V_z or V_z/F (mL/kg)[a,b]							
N	3	3	6	6	6	6	6
Mean (SD)	105.65 (22.402)	117.32 (21.623)	115.64 (28.383)	99.38 (8.722)	100.87 (9.061)	123.22 (17.278)	287.97 (54.069)
Median	115.15	108.64	109.39	99.69	97.74	117.88	285.59
V_{ss} (mL/kg)[a,b]							
n	3	3	6	6	6	6	0
Mean ± SD	98.28 ± 20.940	101.43 ± 13.499	94.12 ± 11.974	84.89 ± 8.335	88.13 ± 11.432	103.15 ± 19.750	NA ± NA
Median	108.63	95.79	97.48	87.94	86.88	93.46	NA
Coefficient of variation	21.31%	13.31%	12.72%	9.82%	12.97%	19.15%	NA
Range	(74.2, 112.0)	(91.7, 116.8)	(76.1, 110.4)	(69.3, 92.8)	(71.9, 101.1)	(92.1, 142.4)	(NA, NA)

Source: Table 4 from summary of clinical pharmacology

Table 58: Summary of guselkumab pharmacokinetic parameters following single SC administration of guselkumab to subjects with psoriasis.

	10 mg SC	30 mg SC	100 mg SC	300 mg SC
Subjects PK evaluable	5	5	5	5
C_{max} (µg/mL)				
N	5	5	5	5
Mean (SD)	0.54 (0.109)	1.14 (0.467)	4.81 (4.255)	18.97 (7.710)
Median	0.50	0.97	3.37	22.70
AUC_{inf} (µg•day/mL)				
N	4	5	5	5
Mean (SD)	14.93 (6.565)	30.26 (15.442)	108.48 (79.215)	510.33 (177.973)
Median	15.11	23.01	84.58	574.62
T_{max} (day)				
N	5	5	5	5
Median	6.03	4.06	3.16	5.27
$T_{1/2}$ (day)				
N	4	5	5	5
Mean (SD)	16.60 (5.024)	14.67 (3.893)	15.89 (3.303)	16.87 (2.429)
Median	17.77	15.75	17.05	16.71
CL/F (mL/day/kg)				
N	4	5	5	5
Mean (SD)	8.55 (4.448)	11.89 (5.069)	11.29 (4.818)	7.50 (3.318)
Median	7.14	11.69	10.34	6.45
V_z/F (mL/kg)				
N	4	5	5	5
Mean (SD)	180.87 (29.262)	231.62 (65.075)	250.76 (111.723)	177.14 (58.997)
Median	177.37	217.06	216.67	159.78

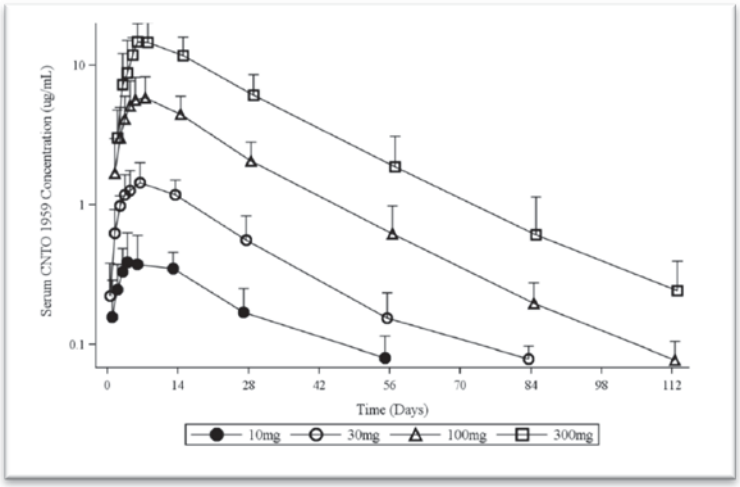
Source: Table7 from summary of clinical pharamacology

In the healthy subjects, estimates of clearance (CL) and apparent volume of distribution at steady-state (Vz) were generally consistent across dose groups and were dose-independent. In subjects with psoriasis, there was no clear relationship between dose and estimates of clearance (CL/F) and volume of distribution (Vz/F). Clearance (CL/F) and volume of distribution (Vz/F) estimates from the 3 mg/kg SC cohort in healthy subjects were generally comparable (within variability) to those observed in psoriasis subjects.

CNTO1959PSO1002 (Single-dose PK study in Japanese subjects with psoriasis)

PSO1002 was a randomized, double-blind, placebo-controlled, ascending dose study in Japanese subjects with moderate to severe plaque psoriasis. A total of 24 Japanese subjects with moderate to severe plaque psoriasis were randomized 5:1 to receive ascending single doses of guselkumab (10, 30, 100, and 300 mg) or placebo, respectively (6 subjects per group). Following a single SC administration of 10, 30, 100, or 300 mg guselkumab, mean Cmax and AUC values increased in an approximately dose-proportional manner. Figure 26 provides the concentration-time profiles of guselkumab in Japanese subjects with psoriasis. PK parameters estimated by non-compartment analysis are listed in
Table 59. Similar to PSO1001, estimates of clearance (CL/F) and volume of distribution (Vz/F) were generally consistent across dose groups and were dose-independent. Further, clearance (CL/F) and volume of distribution (Vz/F) estimates in this study with Japanese psoriasis subjects were comparable to the results from part 2 of PSO1001 in subjects with psoriasis.

Figure 26: Mean (SD) serum guselkumab concentration vs. time profiles following single SC administrations of guselkumab to Japanese subjects with psoriasis.



Source: Figure 6 from clinical study report PSO1001

Table 59: Summary of guselkumab pharmacokinetic parameters following SC administration of guselkumab to Japanese subjects with psoriasis.

		10mg	30mg	100mg	300mg
Total No. Subjects		5	5	5	5
C_{max} (µg/mL)	N	5	5	5	5
	Mean	0.46	1.52	6.14	15.08
	(SD)	(0.192)	(0.561)	(2.290)	(5.154)
	Median	0.42	1.34	5.24	16.52
T_{max} (day)	N	5	5	5	5
	Mean	7.38	5.05	6.78	6.80
	(SD)	(5.166)	(1.415)	(4.122)	(4.096)
	Median	4.021	5.927	6.024	6.033
AUC_{inf} (µg.day/mL)	N	3[a]	5	5	4[b]
	Mean	14.02	40.81	159.94	427.07
	(SD)	(7.766)	(15.825)	(65.231)	(156.689)
	Median	17.29	35.62	133.51	470.27
$T_{1/2}$ (day)	N	3[a]	5	5	4[b]
	Mean	16.38	15.96	17.56	15.56
	(SD)	(6.774)	(5.242)	(3.127)	(3.028)
	Median	15.20	16.28	16.23	15.90
CL/F^c (mL/day/kg)	N	3[a]	5	5	4[b]
	Mean	13.40	10.60	10.00	13.86
	(SD)	(8.733)	(1.894)	(3.199)	(8.196)
	Median	8.62	11.08	10.32	11.90
V_z/F^c (mL/kg)	N	3[a]	5	5	4[b]
	Mean	273.53	243.15	248.44	287.63
	(SD)	(87.038)	(99.109)	(67.817)	(116.325)
	Median	294.48	201.84	242.20	273.24

Source: Table 8 from summary of clinical pharmacology

CNTO1959PSO1003 (Clinical drug interaction study in subjects with moderate to severe plaque-type psoriasis)

Study PSO1003 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]) in subjects with moderate to severe psoriasis. The dosing regimen for the probe cocktail is summarized in Table 60.

Table 60: Dose regimen for the CYP 450 probe substrates used in the clinical DDI study (PSO1003)

CYP Isozyme	Probe	Route	Dose
CYP3A4	midazolam	oral	0.03 mg/kg
CYP2C9	warfarin[a]	oral	10 mg
CYP2C19	omeprazole	oral	20 mg
CYP2D6	dextromethorphan	oral	30 mg
CYP1A2	caffeine	oral	100 mg

a : Vitamin K was co-administered with warfarin.

The probe cocktail was administered on Days 1, 15, and 36; a single SC dose of 200 mg guselkumab administered on Day 8 (Figure 27).

Figure 27: Study scheme for PSO1003

Source: Figure 1 from study protocol for PSO1003

Table 61 summarizes the details of the number of subjects that received treatments on each of the dosing days. The sponsor enrolled a total of 17 subjects with moderate to severe psoriasis, genotyped to exclude poor metabolizers of CYP2C9, CYP2D6, and CYP2C19. Of these 17 subjects, 16 subjects were dosed with the probe on Day 1 (1 week prior to guselkumab dosing), 14 subjects received a single SC dose of 200 mg guselkumab on Day 8, 13 subjects received the probe cocktail on Day 15 (1 week after guselkumab treatment), and 12 subjects received the probe cocktail on Day 36 (4 weeks after guselkumab treatment).

Reference ID: 4123785

Table 61: Number of subjects who were dosed with probe substrates and guselkumab in the clinical DDI study (PSO1003)

	Before guselkumab administration		Post guselkumab administration	
	Day 1	Day 8	Day 15	Day 36
Number of subjects dosed	16	14	13	12
Guselkumab	NA	14	13	12
Probes				
Midazolam*	13	NA	11	11
Warfarin	16	NA	13	12
Omeprazole	16	NA	13	12
Dextromethorphan	16	NA	13	12
Caffeine	16	NA	13	12

* 3 subjects with unverified midazolam dose were excluded by the sponsor; only two of these 3 subjects received guselkumab treatment.

Results:

Assessment of disease severity:
Table 62 summarizes the disease severity based on PASI score of subjects treated with guselkumab in the study. Among the randomized subjects in this study, the baseline median PASI score was 18.45 and all subjects had an IGA ≥3.
By Day 19, only 1 (7.7 %) of 13 subjects achieved PASI75. Even on Day 40, only 2 (16.7%) of 12 subjects achieved PASI75. By Day 64, 9 (75.0%) of 12 subjects achieved PASI75. Similar trends were observed with the improvement in IGA scores (Table 63). The drug interaction assessments were conducted on Day 15 and Day 36 which reflects the period where only modest improvement in disease was observed. Further, drug interaction potential was not assessed around Day 64, when maximal improvement in disease severity was observed.

Table 62: Summary of disease severity of subjects categorized by PASI50/75/90/100 responders and day of assessment.

	Day 19	Day 40	Day 64
Subjects treated	13	12	12
PASI50 responders	5 (38.5%)	9 (75.0%)	11 (91.7%)
PASI75 responders	1 (7.7%)	2 (16.7%)	9 (75.0%)
PASI90 responders	1 (7.7%)	1 (8.3%)	5 (41.7%)
PASI100 responders	0	1 (8.3%)	2 (16.7%)

Table 63: Summary of disease severity of subjects categorized by IGA score category and day of assessment.

	Screening (Baseline)	Day 19	Day 40	Day 64
Subjects treated	16	13	11	11
Subjects with IGA score of cleared (0)	0	0	1 (9.1%)	1 (9.1%)
Subjects with IGA score of cleared (0) or minimal (<=1)	0	1 (7.7%)	4 (36.4%)	8 (72.7%)
Subjects with IGA score of mild or better (<=2)	0	7 (53.8%)	9 (81.8%)	11 (100.0%)

* IGA score from subject # 200004 wasn't available

Assessment of PK of CYP450 probe substrates

The study evaluated PK parameters of all the probe substrates before (Day 1) and after (Day 15 and Day 36) guselkumab administration. Changes in C_{max} and AUC was assessed using geometric mean ratios (GMR) across Day 15/Day 1 and Day 36/Day 1 and the associated 90% CIs of the GMRs. It must be noted that this was an exploratory study and applicant didn't intend to conduct a formal hypothesis testing for the results in this study.

Table 64 summarizes the PK parameters (C_{max} and AUC_{inf}) for each of the probe substrates before (Day 1) and after (Day 15 and Day 36) guselkumab administration. Also included in Table 64 are the GMRs (Day 15/Day 1 and Day 36/Day 1) for C_{max} and AUC_{inf} for each of the probe substrates.

Table 64: Summary of C_{max} and AUC_{inf} for all probe substrates on Day 1 (prior to guselkumab administration), Day 15 and Day 36 in subjects with moderate-to-severe psoriasis.

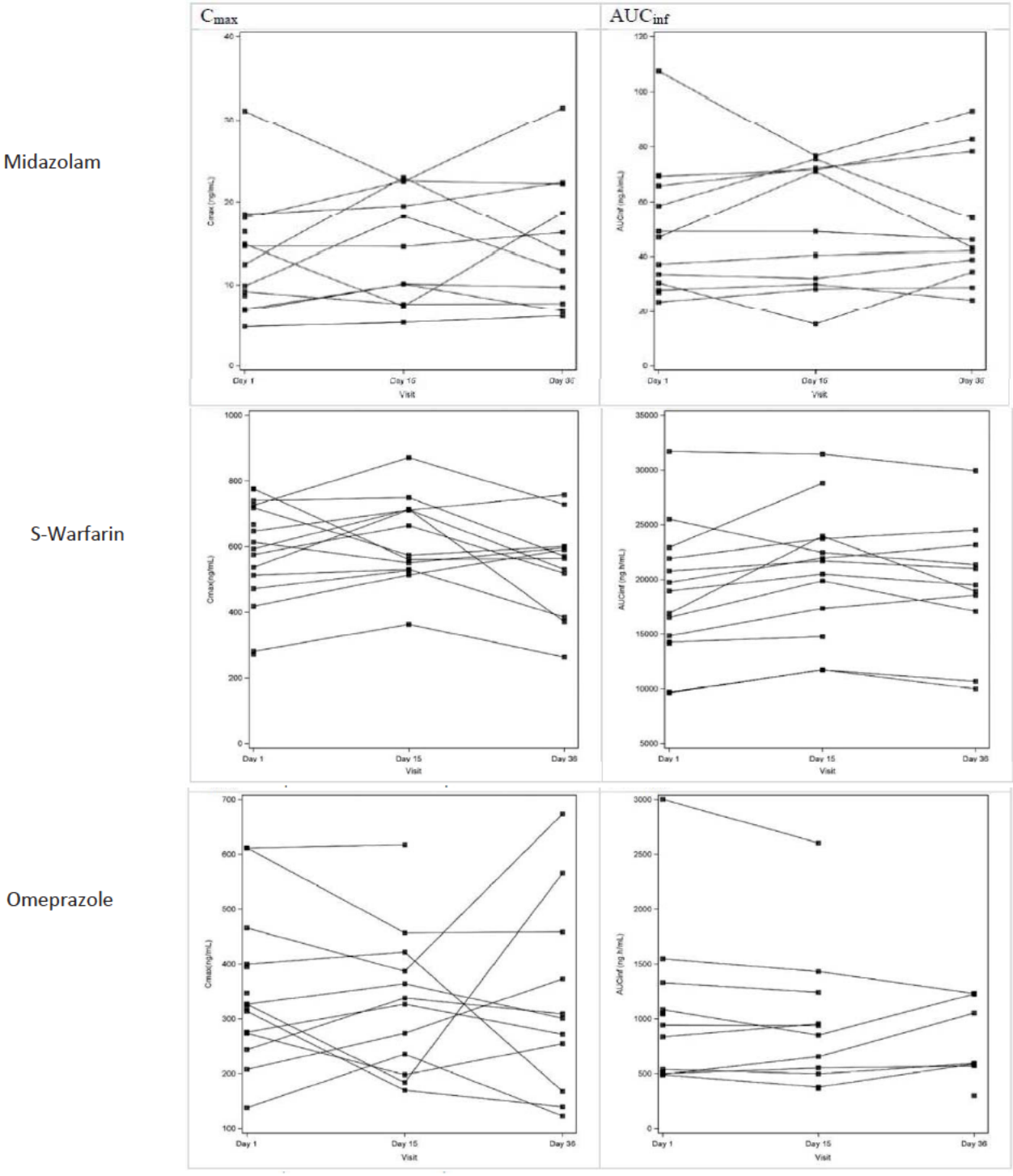
	C_{max} (ng/mL)							
	Day 1		Day 15			Day 36		
	N	Mean (SD)	N	Mean (SD)	GMR (90 % CI)	N	Mean (SD)	GMR (90 % CI)
Midazolam	13	13.22 (6.983)	11	14.62 (6.794)	1.112 (0.752 - 1.645)	11	15.15 (7.964)	1.137 (0.765 - 1.690)
S-Warfarin	16	582.94 (159.702)	13	618.69 (132.677)	1.067 (0.900 - 1.265)	12	540.00 (142.465)	0.904 (0.736 - 1.110)
Omeprazole	15	350.60 (132.607)	12	331.25 (130.839)	0.958 (0.717 - 1.281)	11	330.91 (175.493)	0.955 (0.671 - 1.359)
Dextromethorphan	15	1.78 (2.041)	12	2.12 (2.722)	1.055 (0.457 - 2.434)	11	2.52 (3.266)	1.326 (0.553 - 3.181)
Caffeine	16	2096.25 (533.540)	13	2166.15 (358.900)	1.073 (0.940 - 1.224)	11	2183.64 (499.945)	1.058 (0.888 - 1.262)
	AUC_{inf} (ng.h/mL)							
	Day 1		Day 15			Day 36		
	N	Mean (SD)	N	Mean (SD)	GMR (90 % CI)	N	Mean (SD)	GMR (90 % CI)
Midazolam	13	49.80 (24.007)	11	51.16 (22.885)	1.005 (0.697 - 1.449)	11	51.47 (23.100)	1.039 (0.749 - 1.442)
S-Warfarin	14	18398.20 (6037.814)	13	20774.21 (5871.501)	1.124 (0.903 - 1.398)	11	19522.47 (5725.991)	1.054 (0.817 - 1.361)

Omeprazole	13	1029.90 (686.644)	11	952.75 (646.786)	0.964 (0.613 - 1.517)	7	795.60 (369.740)	1.193 (0.749 - 1.900)
Dextromethorphan	12	23.00 (29.627)	9	17.23 (21.690)	1.127 (0.558 - 2.275)	10	26.43 (33.847)	1.240 (0.464 - 3.314)
Caffeine	16	22766.71 (12311.993)	12	21019.15 (8215.748)	1.004 (0.770 - 1.311)	11	20856.91 (7874.459)	1.018 (0.765 - 1.354)

Source: Applicant's summary of drug interaction analysis from clinical study report for PSO1003

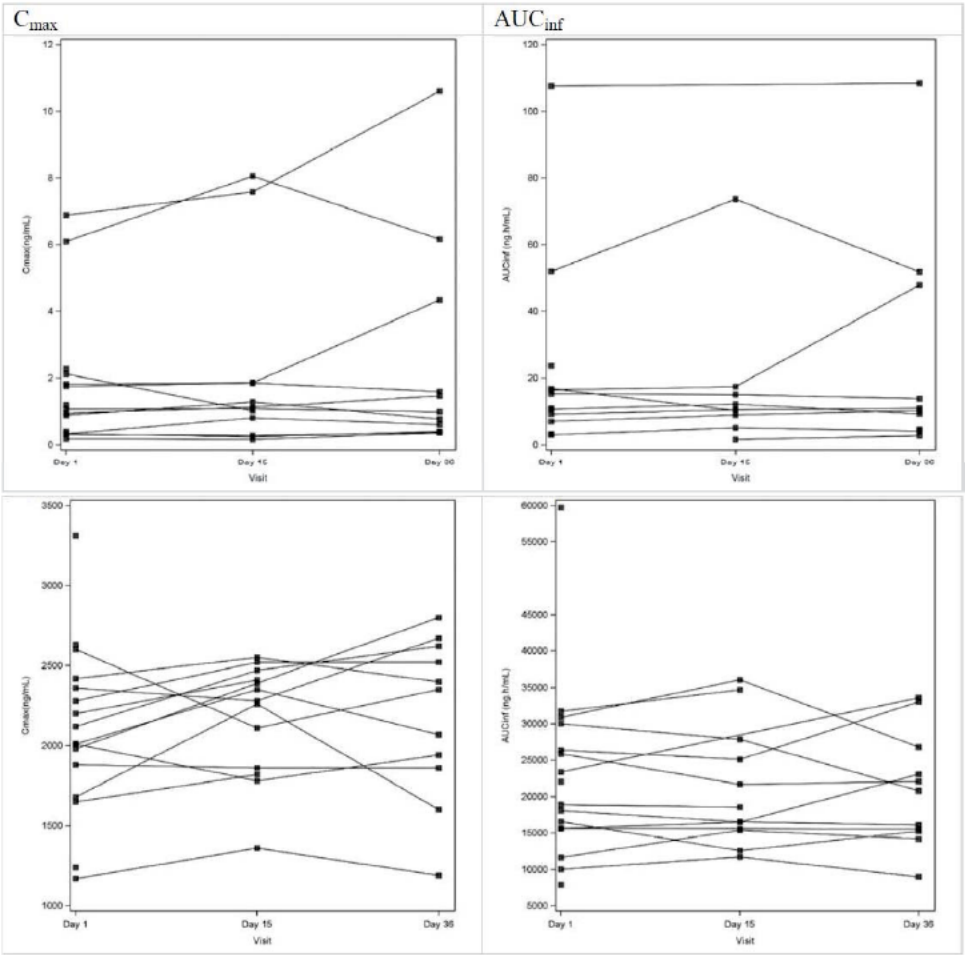
Figure 28 illustrates the change in C_{max} and AUC_{inf} in individual subjects for each of the probe substrates. The changes in C_{max} and AUC_{inf} were variable over time among the individual subjects; however, there were no consistent trends in the data either within-subject or between-subject. Of note for dextromethorphan, there was one individual with 2.9-fold change in AUC_{inf} after guselkumab treatment (Days 36) compared to Day 1.

Figure 28: Plots of individual Cmax and AUCinf estimates for all probe substrates on Day 1 (prior to guselkumab administration), Day 15 and Day 36 in subjects with moderate-to-severe psoriasis.



Dextromethorphan

Caffeine



Summary:

The changes in C_{max} and AUC_{inf} after guselkumab administration were variable across all probe substrates as reflected in the wide 90 % confidence intervals of the GMRs (Day 15/Day 1 and Day 36/Day 1) for C_{max} and AUC_{inf} (Table 64).

For all the probe substrates, the mean GMR for AUC_{inf} was less than 1.25. The upper bounds of the 90 % CI for the GMR (Day 15/Day 1 and Day 36/Day 1) for AUC_{inf} was less than 2.0 for midazolam, S-warfarin, omeprazole and caffeine suggesting that the potential for a clinically relevant drug interaction may be low for compounds metabolized via CYP3A4, CYP2C9, CYP2C19 and CYP1A2 (except for narrow therapeutic index drugs).

However, the upper bound of the 90 % CI for the GMR for dextromethorphan were greater than 2 and greater than 3, respectively for Day 15/Day 1 and Day 36/Day 1. Analysis of the individual data for dextromethorphan revealed that only one individual out of 10 subjects exhibited greater than 2-fold change in AUC_{inf} after guselkumab treatment (Day 36). As a result, we cannot rule out the potential for a clinically relevant drug interaction for compounds metabolized via CYP2D6.

Reviewer's assessment of the subjects excluded from Applicant's DDI analysis:

The review team verified the Applicant's PK analysis using Phoenix 64 (7.0.0.2535) and results were generally in agreement. The Applicant excluded certain subjects from the drug interaction analysis (Table 65). The review team evaluated if the exclusions were appropriate. Exclusions for midazolam, S-warfarin and caffeine were found to be acceptable. For omeprazole and dextromethorphan some of the excluded subjects were evaluated further in a sensitivity analysis and inclusion of these subjects didn't affect the overall conclusion.
The subjects evaluated in the sensitivity analysis are listed below.

- Omeprazole: Subjects 900006 (Day 1, Day 15, Day 36) and 200004 (Day 36)
- Dextromethorphan: Subjects 200004 (Day 1, 15, 36), 500001 (Day 1, Day 15), 900005 (Day 15), 150003 (Day 1) and 150007 (Day 1, Day 15 and Day 36).

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Table 65: List of subjects excluded from the analysis for assessing effect of guselkumab on PK of CYP450 probe substrates (Data source: Clinical study report CNTO1959PSO1003)

Probe Substrate	Subject ID	Day 1		Day 15		Day 36	
		PK Parameters Excluded	Reason for Exclusion	PK Parameters Excluded	Reason for Exclusion	PK Parameters Excluded	Reason for Exclusion
Subjects with PK evaluable		16*		13*		12*	
Midazolam	A71-US10002-200002	all PK parameters	unverified dose	--	--	--	--
	A71-US10002-200004	all PK parameters	unverified dose	all PK parameters	unverified dose	all PK parameters	unverified dose
	A71-US10002-200005	all PK parameters	unverified dose	all PK parameters	unverified dose	--	--
S-warfarin	A71-US10002-200002	AUC_{0-96h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F.	estimated $\%AUC_{\infty,ex}$ >25%	--	--	--	--
	A71-US10005-500001	--	--	--	--	AUC_{0-96h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F.	estimated $\%AUC_{\infty,ex}$ >25%
	A71-US10005-500006	AUC_{0-96h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F.	estimated $\%AUC_{\infty,ex}$ >25%	--	--	--	--
Omeprazole	A71-US10009-900006	all PK parameters	extremely high concentration values; identified as outliers using Dixon test	all PK parameters	extremely high concentration values; identified as cutliers using Dixon test	all PK parameters	extremely high concentration values; identified as outliers using Dixon test
	A71-US10002-200004	--	--	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted R^2 values < 0.80
	A71-US10009-900008	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	insufficient measurable concentration data points	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted R^2 values < 0.80
	A71-US10015-150001	--	--	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	insufficient measurable concentration data points

	A71-US10015-150003	--	--	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	insufficient measurable concentration data points
	A71-US10005-500004	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	insufficient measurable concentration data points	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	insufficient measurable concentration data points	--	--
Dextromethorphan	A71-US10002-200004	all PK parameters	extremely high concentration values; identified as outliers using Dixon test; abnormal PK; $\%AUC_{\infty,ex}$ >25%	all PK parameters	extremely high concentration values; identified as outliers using Dixon test; abnormal PK; $\%AUC_{\infty,ex}$ >25%	all PK parameters	extremely high concentration values; identified as outliers using Dixon test; abnormal PK; insufficient measurable concentration data points
	A71-US10005-500001	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	--	--
	A71-US10009-900005	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	--	--
	A71-US10015-150003	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	--	--	--	--
	A71-US10015-150007	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted $R^2 < 0.80$	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	adjusted R^2 values < 0.80
Caffeine	A71-US10002-200004	--	--	--	--	all PK parameters	abnormal PK (predose concentration [632 ng/mL] > 10% of C_{max})
	A71-US10011-110002	--	--	AUC_{0-24h}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL/F, V_z/F	estimated $\%AUC_{\infty,ex}$ >25%	--	--

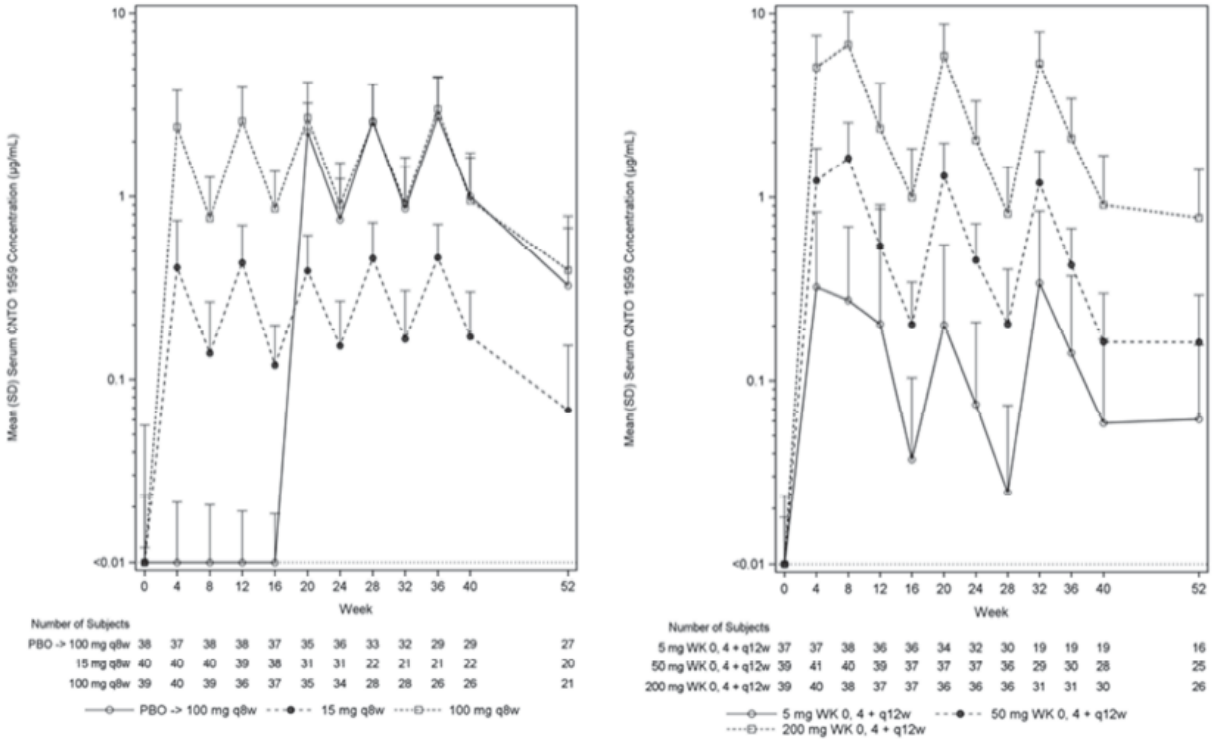
*PK evaluable subjects for midazolam on Days 1, 15, and 36 were 13, 11, and 11, respectively (ie, excluding subjects with unverified dose of midazolam).

CNTO1959PSO2001 (Phase 2 dose ranging study in subjects with Psoriasis)

PSO2001 was a Phase 2, multicenter, randomized, placebo- and active-comparator-controlled, parallel-group, multicenter dose-ranging 7-arm study in subjects with moderate to severe plaque-type psoriasis. A total of 293 subjects with moderate to severe plaque psoriasis were randomized in equal proportions to 1 of 7 of the following treatment groups

- Placebo (at Weeks 0, 4, and 8 and then guselkumab 100 mg at Week 16 and then q8w) (N=42)
- Guselkumab 5 mg (at Weeks 0, 4, and 16 and then q12w) (N=41)
- Guselkumab 15 mg (at Weeks 0, 8, and 16 and then q8w) (N=41)
- Guselkumab 50 mg (at Weeks 0, 4, and 16 and then q12w) (N=42)
- Guselkumab 100 mg (at Weeks 0, 8, and 16 and then q8w) (N=42)
- Guselkumab 200 mg (at Weeks 0, 4, and 16 and then q12w) (N=42)
- Open-label adalimumab 80 mg (at Week 0, 40 mg at Week 1, and then 40 mg q2w) (N=43)

Figure 29: Mean (SD) serum guselkumab concentration through week 52 following SC administrations of guselkumab to subjects with psoriasis.



Source: Figure 7 from clinical study report PSO1001

Results: Serum guselkumab concentrations achieved steady state approximately by Week 16 for all dose groups (Figure 29). Steady state concentrations generally increased in a dose related manner within each of the two dosing intervals (q8w and q12w). There was no evidence of substantial accumulation in serum guselkumab concentrations over time consistent with the t1/2 of guselkumab values of approximately 18 days. Summary of trough serum guselkumab concentrations at Week 40 are listed in Table 66.

Table 66: Summary of trough serum guselkumab concentrations (µg/mL) at Week 40 in study CNTO1959PSO2001.

Dosing Regimen	Guselkumab q8w		Guselkumab Week 0, 4 + q12w		
Dose	15 mg	100 mg	5 mg	50 mg	200 mg
N	22	26	19	28	30
Mean (SD)	0.17 (0.130)	0.95 (0.686)	0.06 (0.109)	0.16 (0.138)	0.91 (0.779)
Median	0.13	0.93	0.02	0.13	0.79
Range	(0.0; 0.6)	(0.1; 3.1)	(0.0; 0.4)	(0.0; 0.6)	(0.1; 3.3)
IQ range	(0.09; 0.23)	(0.48; 1.31)	(0.01; 0.03)	(0.07; 0.21)	(0.31; 1.05)

Key: IQ=inter-quartile; N=sample size; q8w=every 8 weeks; q12w=every 12 weeks; SD=standard deviation
Source: Table 9 from summary of clinical pharmacology

CNTO1959PSO3001 (Pivotal Phase 3 efficacy study in subjects with Psoriasis)

PSO3001 was a Phase 3, randomized, double-blind, placebo and active comparator-controlled, multicenter, study with moderate to severe plaque-type psoriasis.
A total of 837 subjects with moderate to severe plaque psoriasis were randomized at Week 0 in a ratio of 2:1:2 to 1 of 3 treatment groups:

- Guselkumab 100 mg at Weeks 0, 4, and 12 and q8w thereafter through Week 44 (N=329)
- Placebo beginning at Week 0 followed by guselkumab 100 mg at Week 16 and Week 20 and q8w thereafter through Week 44 (N=174)
- Adalimumab (80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and q2w thereafter through Week 47 (N=334)

Results: Serum guselkumab concentration achieved steady state by Week 20. Mean steady-state trough serum guselkumab concentration was 1.23 µg /mL at Week 20; trough serum guselkumab concentrations were maintained at steady state through Week 44. There was no evidence of accumulation in serum guselkumab concentrations overtime.

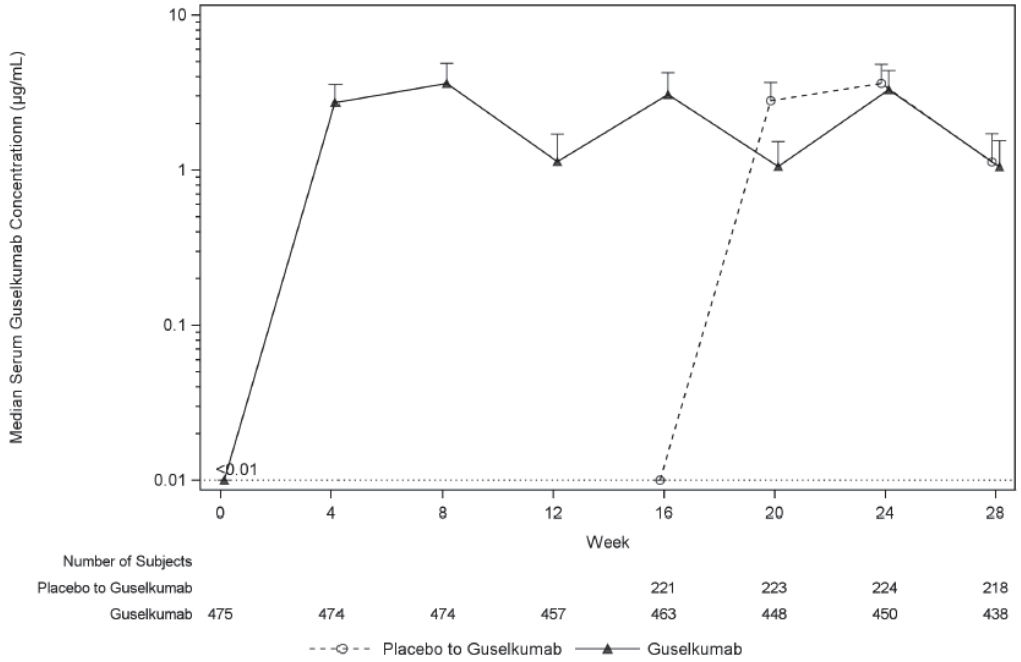
CNTO1959PSO3002 (Pivotal Phase 3 efficacy study in subjects with Psoriasis)

PSO3002 was a Phase 3, randomized, double-blind, placebo and active comparator-controlled, multicenter study in subjects with moderate to severe plaque-type psoriasis. The study consisted of 3 phases: placebo- and active-comparator-controlled treatment, randomized withdrawal and retreatment, and open-label guselkumab treatment.
A total of 992 subjects with moderate to severe plaque psoriasis were randomized in a ratio of 2:1:1 to 1 of 3 arms:

- Guselkumab 100 mg at Weeks 0, 4, 12, and 20 (N=496)
- Placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20 (N=248)
- Adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and q2w thereafter through Week 23 (N=248)

For subjects randomized to guselkumab, serum guselkumab concentration achieved steady state by Week 20, with mean steady-state trough serum guselkumab concentration of 1.15 µg /mL at Week 20 (Figure 30).

Figure 30: Median and interquartile range of serum guselkumab concentration vs. time profiles through Week 28 in subjects treated with guselkumab in study PSO3002.



Source: Figure 9 from summary of clinical pharmacology

CNTO1959PSO3003 (Phase 3 efficacy study in psoriasis subjects with inadequate response to ustekinumab treatment)

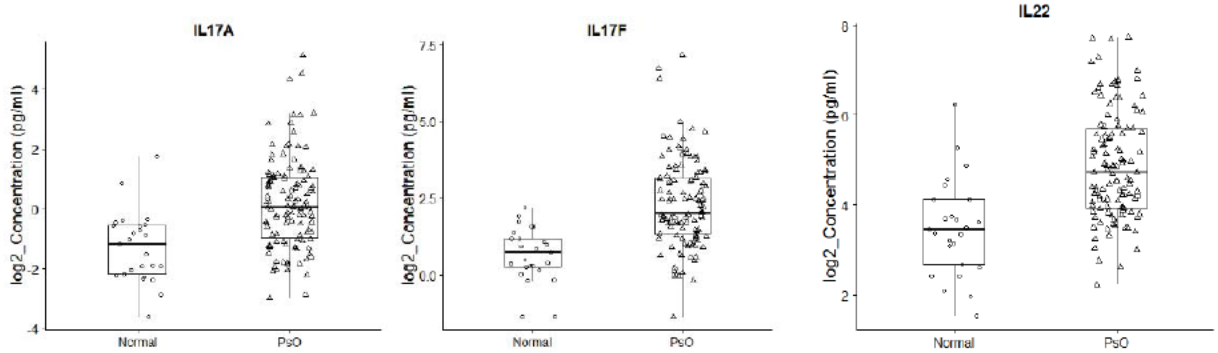
PSO3003 was a Phase 3, randomized, double-blind, multicenter study in subjects with moderate to severe plaque-type psoriasis with inadequate response to ustekinumab. The study consisted of 3 phases: open-label ustekinumab treatment, blinded active treatment, and follow-up. A total of 871 subjects with moderate to severe plaque psoriasis received open-label ustekinumab 45 mg or 90 mg (according to the subject's baseline [Week 0] weight < or ≥100 kg) at Week 0 through Week 16. At Week 16, 268 subjects with IGA ≥2 were randomized (135 subjects in the guselkumab group, 133 subjects in the ustekinumab group); 585 subjects with an IGA=0 or 1 (cleared or minimal disease) continued to receive open-label ustekinumab q12w from Week 16 through Week 48.
For subjects who were randomized to guselkumab, steady state of serum guselkumab concentration appeared to be achieved by Week 28 (i.e., 12 weeks after the first SC administration of guselkumab), with a mean trough serum guselkumab concentration of 1.08 µg /mL at Week 28.

13.4.4. Pharmacodynamics

13.4.4.1. Effect of guselkumab treatment on serum IL-17A, IL-17F and IL-22 levels in subjects with psoriasis

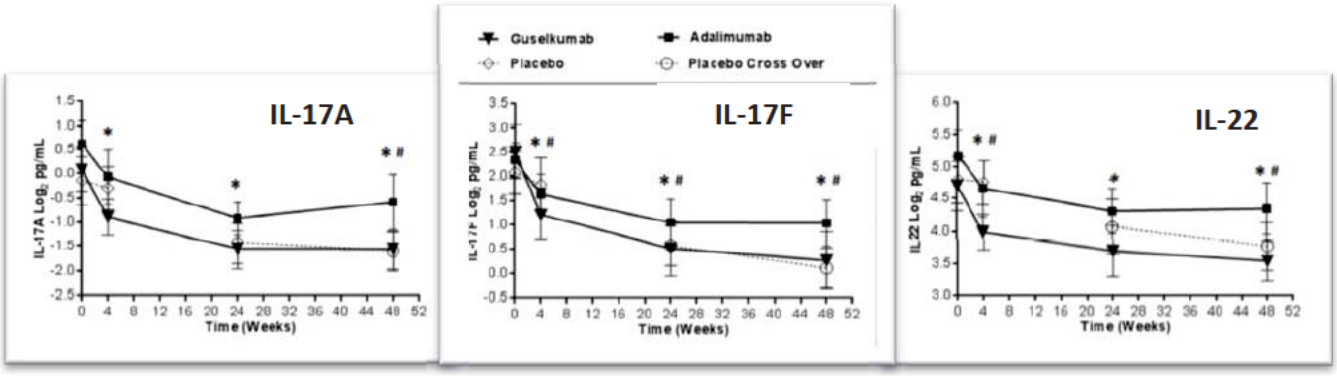
The Applicant evaluated serum levels of multiple cytokines (including IL-17A, IL-17F, IL-22, IL-23) in subjects with psoriasis in studies PSO2001 and PSO3001. In addition the Applicant also evaluated the levels of these analytes in a small sample of healthy subjects (N=25). IL-17A, IL-17F and IL-22 levels were lower in healthy subjects than in subjects with psoriasis (Figure 31). Additionally, IL-17A, IL-17F, and IL-22 were significantly lower at Weeks 24 and Week 48 ($p \leq 0.001$) in guselkumab treated subjects compared to in placebo-treated subjects (Figure 32). Similar trends were observed in study PSO2001. Based on these results, the Applicant concluded that these biomarkers are related to the disease state in psoriasis patients and could be potential biomarkers of response to guselkumab.

Figure 31: Serum levels of IL-17A, IL-17F and IL-22 in healthy subjects versus subjects with psoriasis.



Source: Modified from figure 2 from Immunology Biomarker Exploratory Report for CNTO1959PSO3001

Figure 32: Serum levels of IL-17A, IL-17F and IL-22 over time in guselkumab-treated subjects compared with placebo-treated group from study PSO3001.



Source: Modified from figure 4 and 5 from Immunology Biomarker Exploratory Report for CNTO1959PSO3001

Reviewer comments:

However, there are several limitations in the analyses, making it difficult to draw definitive conclusion from the study results.
These include:

- *All the serum analyses were exploratory with protein levels determined in Phase 2 studies and only in small subsets of patients (N = 40 per arm) from one of the Phase 3 study (PSO3001).*
- *The comparison of the protein levels between psoriasis patients and healthy subjects was based on a small sample of healthy individuals (n=25 for healthy versus n = 118 for psoriasis subjects).*

Further, the sponsor hasn't provided data to indicate that changes in these serum biomarkers exhibit a correlation with the doses of guselkumab administered. Therefore it is unclear what level of change in these biomarkers would reflect a change in the efficacy endpoint.

13.4.4.2. Effect of guselkumab treatment on histology and gene expression profiles of skin biopsy specimens in subjects with psoriasis

In their phase 1 single dose study (PSO1001: Arm 2 subjects with psoriasis), the applicant conducted histologic analysis and evaluated changes of gene expression in skin biopsy specimens obtained from subjects dosed with guselkumab compared to placebo. Skin biopsy specimens were collected before administration of guselkumab (baseline) and after dosing at Weeks 1 and 12.

For histological analysis, the applicant assessed reductions in epidermal thickness, T-cell density, and dendritic cells.

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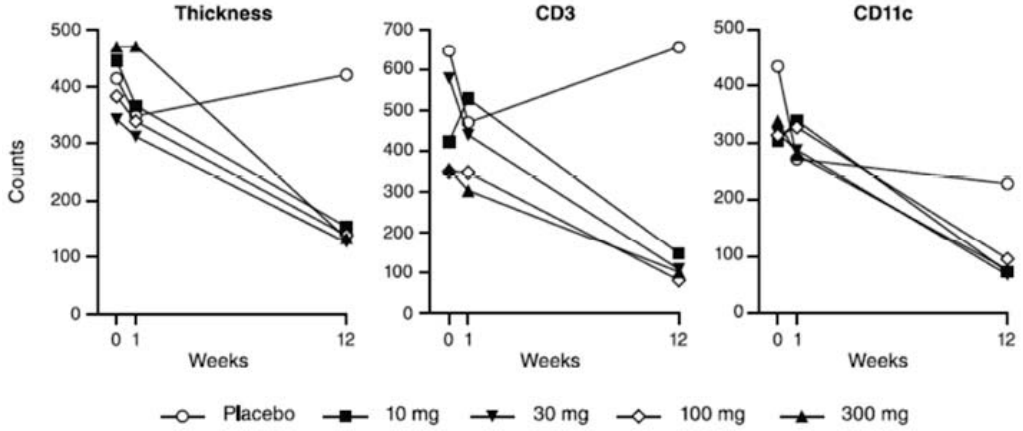
Figure 33 summarizes the histological analysis at baseline and at weeks 1 and 12 in guselkumab treated or placebo treated subjects. At Week 12, statistically significant reductions in epidermal thickness and T-cell and inflammatory CD11c dendritic cells (DC) counts were observed for each guselkumab dose group compared with baseline (p<0.05 each).

Figure 33: Histological analysis (Mean Epidermal Thickness, T-cell and Myeloid DC expression) from lesional skin biopsy specimens at baseline and after guselkumab or placebo treatment at Weeks 1 and 12 from Study PSO1001.



Reviewer comments: Any conclusions drawn from these histological and transcriptomic analysis are limited due to the exploratory nature of the analysis. These analyses are from a single study following one dose of guselkumab and have not been replicated. We are also unable to draw conclusions on potential dose dependent pharmacodynamic effects as the data is combined across two dose groups (100 mg and 300 mg).

13.4.5. Immunogenicity

13.4.5.1. Immunogenicity incidences of ADA and NAb

The overall incidence of antibodies to guselkumab through up to Week 52 after exposure to guselkumab was 5.5% (N=96) across the Phase 2 and phase 3 studies. Of the subjects who developed anti-drug antibodies to guselkumab, 7 of 96 subjects (7.3 %) were positive for neutralizing antibodies (NAbs). The overall immunogenicity incidences for developing ADA and NAb in each of the individual Phase 2/3 studies are summarized in Table 67.

Table 67: Summary of immunogenicity incidence for Phase 2 and Phase 3 studies

	PSO2001	PSO3001	PSO3002	PSO3003
ADA No. of Subjects (%)	15/240 (6.2%)	26/492 (5.3%)	57/869 (6.6 %)	4/130 (3.1%)
NAb No. of Subjects (%)	0	5/26 (19.2%)	2/57 (3.5%)	0

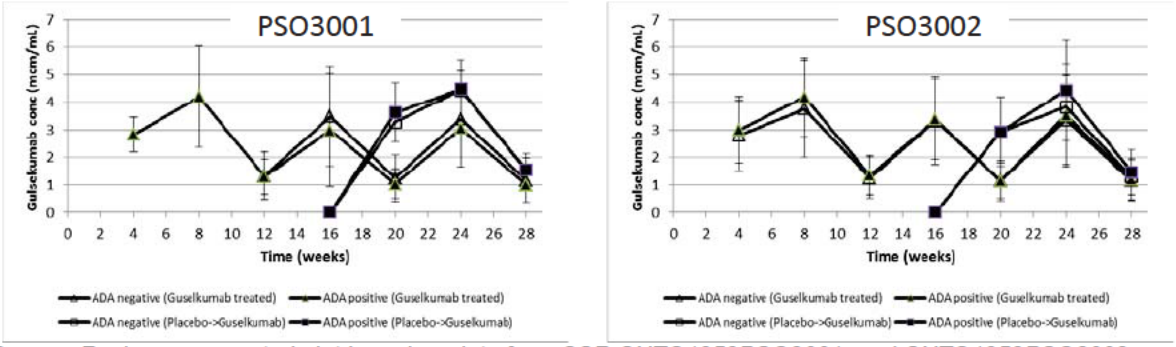
Source: Data from CSR CNTO1959PSO2001, CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003

13.4.5.2. Impact of immunogenicity on PK

The applicant combined the PK and immunogenicity data from the pivotal PSO3001 and PSO3002 studies for evaluation of immunogenicity effects. The applicant justified this based on the identical design of both studies through Week 28 with respect to the initial guselkumab group and the placebo-crossover group. The review team has also reviewed the results from both studies separately to confirm that the conclusions are the same.

Inter-subject comparison: ADA+ vs. ADA- subjects
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. Mean serum guselkumab concentrations in subjects who were positive for antibodies to guselkumab were generally similar to those at respective sampling time points in subjects negative for antibodies to guselkumab (Figure 34). Table 68 compares steady state concentrations at week 28 in ADA+ subjects with varying ADA titers relative to ADA- subjects across studies PSO3001 and PSO3002. These results suggest that antibody titer didn't appear to have a consistent effect on PK of guselkumab across ADA+ subjects.

Figure 34: Comparison of serum guselkumab concentration in subjects with psoriasis who were ADA+ and ADA- in Phase 3 studies PSO3001 and PSO3002.



Source: Reviewer generated plot based on data from CSR CNTO1959PSO3001, and CNTO1959PSO3002

Table 68: Steady state trough concentrations of guselkumab at Week 28 in ADA positive and ADA negative subjects from guselkumab treatment arm in Phase 3 studies PSO3001 and PSO3002. ADA titer information is based on ADA status at Week 28.

Study		ADA negative	ADA positive	Peak Titers for Antibody Positive Subjects			
				10	> 10 to < 100	≥100 to <1000	≥1000
PSO3001	N	269	16	1	5	8	2
	Mean (SD)	1.171 (0.804)	1.006 (0.545)	0.461 (-)	0.989 (0.551)	1.063 (0.6431)	1.089 (0.026)
PSO3002	N	407	31	5	17	7	2
	Mean (SD)	1.158 (0.748)	1.193 (0.752)	1.144 (0.242)	1.242 (0.852)	1.357 (0.722)	0.322 (0.455)

Source: Reviewer generated table based on data from CSR CNTO1959PSO3001, and CNTO1959PSO3002

Subject level comparison by ADA+ subjects
This reviewer also assessed the impact of immunogenicity on PK at the subject level using the following approaches:

- Comparison of the steady state trough concentration data between ADA+ samples and ADA- samples within each ADA+ subject.
- Comparison of the concentration data at the time of ADA+ observation in ADA+ subject with the median concentration for the respective timepoint in the ADA- subjects

ADA was deemed to impact PK in a given individual when guselkumab concentrations for ADA+ samples were lower than the concentrations for ADA- samples in a given individual and the concentration in a given individual was lower than the median concentration for the respective time point for the ADA- subjects who received similar guselkumab dose regimen.
Table 69 summarizes the assessment results of the impact of immunogenicity on PK based on the reviewer's evaluation of the individual concentration-time profile in the two pivotal Phase 3 studies (PSO3001 and PSO3002). Among the 26 ADA+ subjects in PSO3001, a negative impact of ADA on PK was observed in 16 subjects while no impact was observed in 10 subjects. In study PSO3002, among the 46 ADA+ subjects (in the placebo-crossover and guselkumab treated groups), the impact of immunogenicity on PK could not be assessed in 19 subjects and no impact was found in 9 subjects. A negative impact of ADA on PK was observed in the remaining 18 subjects in Study PSO3002. One subject (RU00380-20581) in the guselkumab treated cohort in PSO3002 exhibited high ADA titer (1:1280 to 1:10240) starting at Week 16 and was also positive in the NAb assay at subsequent timepoints. In this individual, guselkumab concentrations were low or below LLOQ starting at Week 20 through Week 44 indicating a remarkable impact of ADA on guselkumab PK. These results indicate that presence of ADA can influence the PK of guselkumab in certain subjects.

Table 69: Summary of the impact of immunogenicity on PK based on the reviewer's evaluation of the individual concentration-time profile in the two pivotal Phase 3 studies (PSO3001 and PSO3002).

		Negative impact	No Impact	Impact cannot be determined#
PSO3001	ADA+	16/26 (61.5%)	10/26 (38.5%)	-
	NAb+	4/5 (80%)	1/5 (20%)	-
PSO3002	ADA+	18/46 (39 %)	9/46 (19.6%)	19/46 (41.3 %)
	NAb+	2/2 (100 %)	-	-

Reasons include undetectable trough concentration at the reference time point, insufficient samples for overall assessment, ADA+ at Week 0 of the maintenance study, and undetectable concentrations for all trough concentration samples.

13.4.5.3. Impact of immunogenicity on efficacy

Analogous to the evaluation of effect of immunogenicity on PK, the applicant combined the efficacy and immunogenicity data from the pivotal PSO3001 and PSO3002 studies for evaluation of immunogenicity effects. The applicant justified this based on the identical design of both studies through Week 28 with respect to the initial guselkumab group and the placebo-crossover group. This reviewer has also reviewed the results from both studies separately and the overall conclusions are the same.

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Table 70 summarizes the clinical responses (IGA0/1) at Week 28 in ADA+ and ADA- subjects in the pivotal phase 3 studies. The development of antibodies to guselkumab wasn't associated with a reduction in the efficacy of guselkumab in either study. However, in looking at the individual data there was one subject (Subject # RU00380-20581) in study PSO3002 with high ADA titer (1:1280 to 1:10240) who exhibited loss of efficacy. Further in the 7 subjects who were positive for neutralizing antibodies, loss of clinical response was observed in 2 subjects while in the other 5 subjects there was no loss of clinical response (IG0/1).

Table 70: Summary of clinical responses (IGA0/1) at Week 28 in ADA+ and ADA- subjects in the Phase 3 study PSO3001 and PSO3002.

Study CNTO1959PSO3001					Peak Titers for Antibody Positive Subjects			
Treatment	Endpoint		ADA negative	ADA positive	10	> 10 to < 100	≥100 to <1000	≥1000
Placebo -> Guselkumab	IGA 0/1	N	158	7	0	3	2	2
		Subjects in response	139 (88.0%)	7 (100.0%)	-	3 (100%)	2 (100%)	2 (100%)
Guselkumab		N	308	19	1	5	11	2
		Subjects in response	248 (80.5%)	17 (89.5%)	1 (100%)	5 (100%)	9 (81.8%)	2 (100%)

Study CNTO1959PSO3002					Peak Titers for Antibody Positive Subjects			
Treatment	Endpoint		ADA negative	ADA positive	10	> 10 to < 100	≥100 to <1000	≥1000
Placebo -> Guselkumab	IGA 0/1	N	220	11	4	4	2	1
		Subjects in response	180 (81.8%)	10 (90.9%)	4 (100%)	4 (100%)	1 (50.0%)	1 (100%)
Guselkumab		N	457	35	5	20	8	2
		Subjects in response	380 (83.2%)	32 (91.4%)	5 (100%)	18 (90%)	8 (100%)	1 (50%)

13.4.5.4. Impact of immunogenicity on Injection Site Reactions (ISR)

A definitive conclusion can't be made about the associations between presence of antibodies to guselkumab and the development of ISRs due to the small number of ADA+ subjects who had ISRs. Further, antibody titer levels also didn't exhibit any consistent correlation with the development of ISRs was observed.

In Study PSO3001, 3 (11.5%) of the 26 subjects who were ADA+ had an ISR, while 24 (5.2%) of the 466 subjects who were ADA- had ISRs. In Study PSO3002, 5 (10.9%) of the 46 subjects

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who were ADA+ had an ISR, while 37 (5.5%) of the 677 subjects who were ADA- had ISRs. Across both studies, the proportion of ADA+ subjects who exhibited ISRs appeared to be greater compared to ADA- subjects, although a definite conclusion can't be reached due to the small number of subjects who had ISRs.

13.4.6. Population PK Analysis

13.4.6.1. Dose selection

Dose selection for Phase 3 studies was based on the PSO2001 Phase 2 dose ranging study. The Phase 2 study was a randomized, multicenter, placebo- and active comparator-controlled in subject with psoriasis, which studied the following regimens: placebo administered subcutaneously at Weeks 0, 4, and 8 followed by crossover to guselkumab 100 mg at Week 16 and every 8 weeks (q8w) thereafter through Week 40; guselkumab 5 mg , 50 mg or 200 mg administered subcutaneously at Weeks 0, 4, 16 and every 12 weeks (q12w) through Week 40; guselkumab 15 mg and 100 mg administered subcutaneously at Weeks 0, 8, and 16 and q8w through Week 40; adalimumab 80 mg administered subcutaneously at Week 0, 40 mg at Week 1, and q2w thereafter through Week 39.

13.4.6.2. Population Pharmacokinetic and Pharmacodynamic Exposure-Response analysis

The sponsor performed population PK (popPK) and pharmacodynamic (PD) exposure-response analyses in patients to:

- Establish a PopPK model and quantify population PK parameters, including typical values and random variability estimates for guselkumab
- Identify covariates which significantly influence guselkumab PK in adult subjects with psoriasis (PSO) and quantify their effects;
- Evaluate the necessity of covariate-based dosing adjustment, if any, for guselkumab in adult psoriatic patients.

Methods
Population Pharmacokinetic analysis
The popPK analysis was based on concentration data from a Phase 2 (PSO2001) and two Phase 3 studies (PSO3001 and PSO3002) in psoriasis patients. Blood samples for measuring serum guselkumab concentrations were collected during visits at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 36, and 44 in the double-blinded treatment phase. Table 71 shows a summary of the data included in the final dataset used for popPK analysis. Of note, few samples were available during the absorption phase following dosing, and the data that was available came solely from placebo patients who were re-randomised to guselkumab at week 16.

Reference ID: 4123785

Table 71: Population pharmacokinetic analysis dataset.

Items Number of subjects in original dataset	PSO2001 238	PSO3001 494	PSO3002 727	Total 1459
Data in original Dataset				
Number of subjects in original dataset	238	494	727	1459
Number of PK records in original dataset	2301	4589	8428	15318
Number of missing PK records	0	10	18	28
Number of PK records excluded for missing sampling date	0	12	31	43
Number of PK records excluded for sampling time later than dosing time	0	68	82	150
Number of pre-dose PK samples	235	502	961	1698
Number of pre-dose PK samples>LLOQ	7	19	19	45
Number of post-dose BQL samples	52	35	281	368
Number of outlier PK records exclude from final dataset	11	0	6	17
Data in Final Dataset				
Number of subjects included in final dataset	238	492	724	1454
Number of PK records included in final dataset	2003	3962	7049	13014
Number of subjects with positive immunogenicity in final dataset	7	26	46	79
Number of dosing records with imputed dosing times	0	35	33	68

Source: Applicant's Population PK Report, Attachment 1, Page 55

The applicant's primary model development began with the pre-specified base model development based on existing information from previous studies. The pre-specified PopPK model was developed based on Phase 2 data and used a linear one-compartment model with first-order absorption, parameterized in apparent clearance (CL/F) and volume of distribution (V/F) and absorption rate constant (Ka) with inter-subject variance on CL/F and V/F and proportional and additive random unexplained variability. Effects of body weight on CL/F and V/F were included in the structure pharmacokinetic model *a priori*. The pre-specified base model with addition of inter-subject variance on Ka was then fitted to the observed data, with all parameters re-estimated. A stable full covariate model on CL/F was initially developed using all covariates of interest that could be reliably estimated from the data, and then reduced to include only covariates with effect sizes of at least 10%.

Covariates tested
The applicant evaluated covariates based on rank order starting with the most important one: immune response (subject-level and time-varying), age, sex, race, baseline albumin, diabetes comorbidity, baseline body mass index (BBMI), baseline body surface area (BBSA), height, baseline PASI, baseline IGA, disease duration, presence of PsA, concomitant corticosteroid use, concomitant nonsteroidal anti-inflammatory drugs (NSAID) use, other concomitant medications, baseline C reactive protein (CRP), concurrent comorbidities (hypertension, hyperlipidemia), past use of biologics, past use of methotrexate, past use of cyclosporine, creatinine clearance, smoking status, alcohol use, other selected laboratory measurements (AST, ALT, ALP, and WBC).
Results
Population pharmacokinetic analysis
The applicant's final base model included an estimate of inter-individual variability on Ka, the structural base model was based on pre-specified pharmacokinetic model. A one-compartment linear model with first-order absorption and first-order elimination was identified with inter-individual variability on Ka, CL/F, and V/F, was found to reasonably describe the observed data. The applicant included correlation terms between CL/F and V/F. The unexplained random variability was described by a combination additive and proportional error model. However, the applicant fixed additive residual error at 0.00289 µg/mL based on a calculation of the probability distribution characteristic associated with lower limit of quantification of 0.01 µg/mL.

The applicant explored covariate effects after including the correlation between CL//F and V/F. Covariates effects that remained following correlation analysis were included in the covariate model development. Apart from the effect of body weight on V/F, covariates were tested only on CL/F since this is the primary pharmacokinetic parameter of interest. The full model was then reduced to include only covariates with mean effect sizes corresponding to at least 10% of the typical values of the respective PK parameter. Effects of body weight (BWT) on CL/F and V/F, and diabetes comorbidity (DIAB) and race (Caucasian versus non-Caucasian) on CL/F met this criterion. All other covariates with relatively small effects were removed from the full covariate model. The parameters of the final reduced population PK model are summarized in Table 72.

Reference ID: 4123785

Table 72: Parameter Estimates in the Final Reduced Population Pharmacokinetic Model

Parameters[a]	Estimate[b]	95th Confidence Interval	Magnitude of Change[c]
CL/F (L/day)[d]	0.516 (1.19)	0.504-0.528	--
Baseline body weight (BWT) on CL/F	0.998 (4.37)	0.913-1.08	-14.1% – 14.8%
Diabetes (DIAB) on CL/F	1.12 (2.41)	1.07-1.17	12%
Non-Caucasian (RACE) on CL/F	1.11 (1.56)	1.08-1.14	11%
V/F (L)[e]	13.5 (1.08)	13.2-13.8	--
Baseline body weight on V/F	0.829 (4.61)	0.754-0.904	-11.9% – 12.1%
Ka (1/day)	1.11 (14.1)	0.804-1.42	--
IIV of CL/F (%)	35.6 (6.54) [4.30]	33.3-37.9	--
IIV of V/F (%)	28.0 (9.85) [15.4]	25.2-30.6	--
IIV of Ka (%)	129 (22.9) [74.7]	96-156	--
Correlation between IIV of CL/F and V/F	0.834	--	--
Proportional residual error (CV%)	20.0% (2.44)	19.0%-21.0%	--
Additive residual error (µg/mL)	0.00289 (--)	--	--

[a] CL/F= apparent clearance; V/F= apparent volume of distribution; Ka= first-order absorption rate constant; IIV= inter-individual variability; calculated as $(\text{variance})^{1/2}*100\%$.

[b] Mean (RSE%) [Shrinkage %] estimates by NONMEM from the final PK dataset.

[c] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, i.e., % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population.

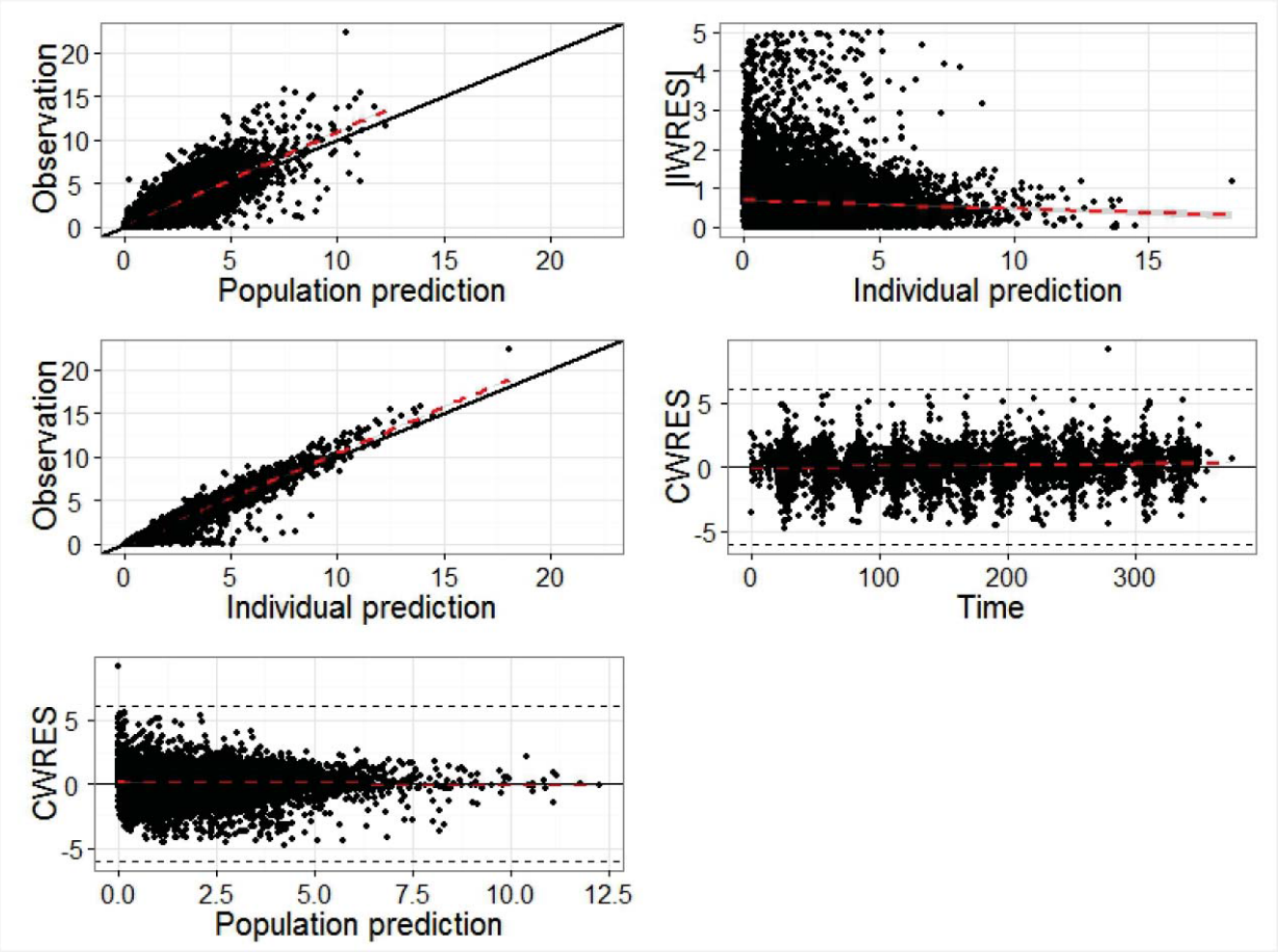
[d] $CL/_F = 0.516 \times (\frac{BWT}{87.1})^{0.998} \times 1.12^{DIAB} \times 1.11^{RACE}$

[e] $V/_F = 13.5 \times (\frac{BWT}{87.1})^{0.829}$

(*Source: Applicant's popPK report, page 42, Table 8)*

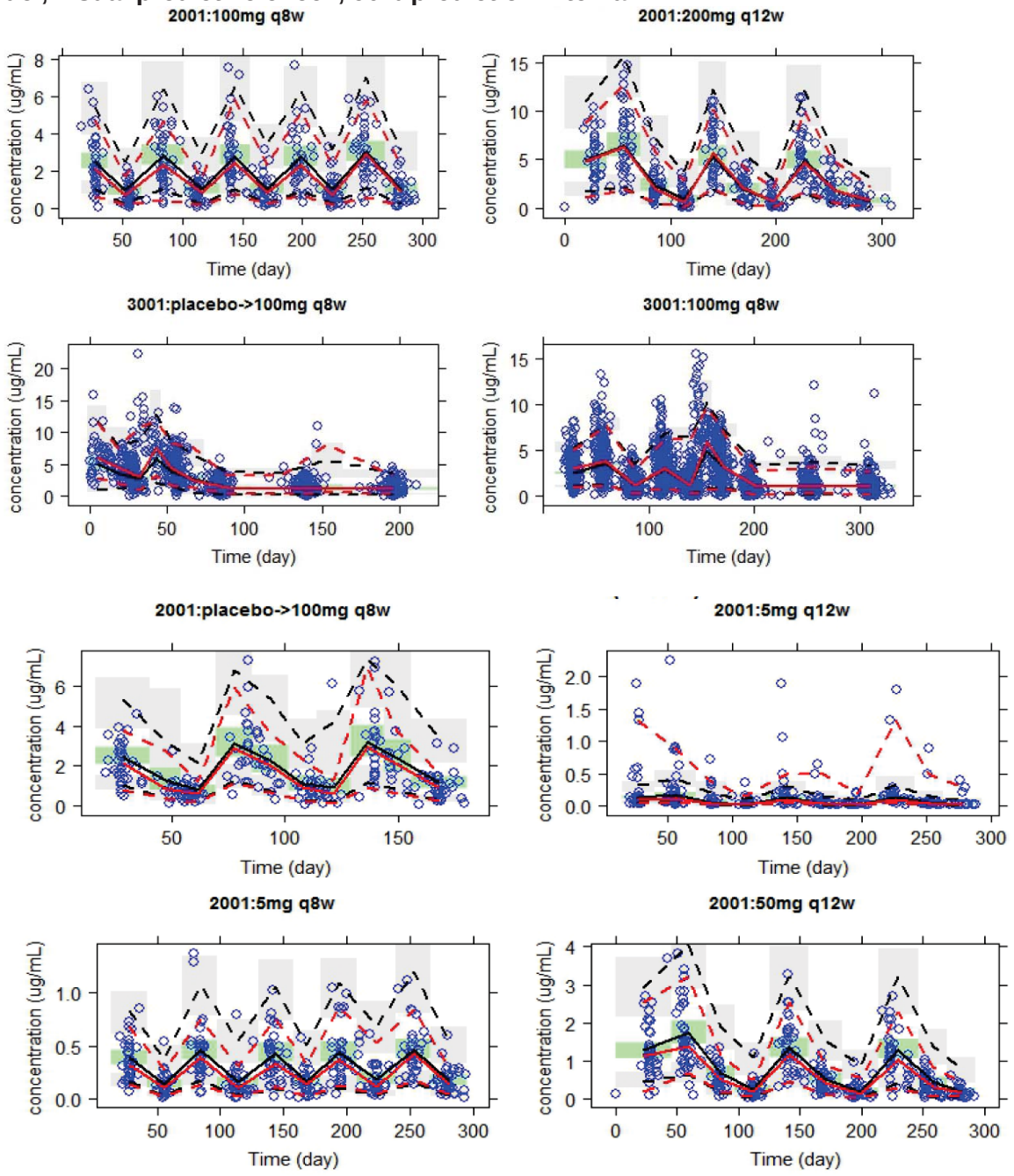
The applicant evaluated the performance of the final popPK model through goodness of fit plots (Figure 35) and using VPC with stratifications by study and treatment groups (Figure 36).

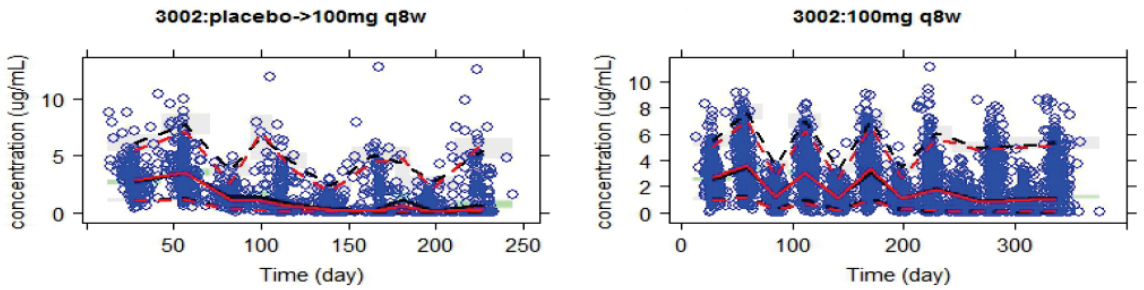
Figure 35: Basis Goodness-of-fit Plots for Final Reduced Population Pharmacokinetics Model.



Key: |iWRES|= absolute individual weighted residuals; CWRES=conditional weight residuals. The black solid line is the line of identity or the zero line, and the red dashed line is the trend line. The black dashed line represent |CWRES|=6. The black circles are the observations. Units: Observations or Predictions= µg/ml; Time= day

Figure 36: Observed vs Simulated Serum Guselkumab Concentration-Time Profiles Stratified by Study and Treatment Groups for Final Reduced Population Pharmacokinetic Model, visual predictive check, 90% prediction interval.





Key: q8w= every 8 weeks, q12 w= every 12 weeks. Blue circles are the observations. Red solid and dashed lines are the 50th and 5th/95th percentile of the observations. Black solid and dashed lines are the 50th and 5th/95th percentile of the model predictions. Green areas are the 90% confidence interval (CI) of the simulated median trend. Grey areas are the 90% CI of the simulated trends at 5th and 95th percentiles. (Source: Applicant's popkPK report, page 45-46, Figure 3)

Reviewer's comments:
The sponsor's Pop-PK model provides reasonable description of guselkumab concentrations for individual predictions as shown in the goodness of fit plots. Visual inspection shows that the model reasonably predicts individual data over a range of concentrations in the studies involved. Inclusion of inter-occasional variability in the applicant's model improved the fit, without significant changes in parameter estimates and visual predictive check results. There was observed change in CL/F attributable to body weight which ranged from –14.1% to +14.8% relative to the median CL/F estimate (ie, a 28.9% difference) when body weight increased from the 25th percentile (74.8 kg) to the 75th percentile (100 kg) of the population values.
Even though the impact of anti-drug antibodies did not have any influence on the CL/F when evaluated as time-varying variable on CL/F, the limited data in the popPK analysis for anti-drug antibodies as well as limitation with the assay prevents an accurate assessment of the potential impact of anti-drug antibodies on guselkumab exposure.
Body weight was a significant covariate on clearance. However, with the choice of 100 mg at Weeks 0 and 4 followed by 100 mg q8w dosing regimen, the efficacy response has approached the plateau of the exposure-response curve by week 20 of efficacy data. Thus, the incremental benefit with body weight-based dosing or a higher dose for patients with a higher body weight may be limited. Hence, the proposed dosing regimen regardless of body weight is acceptable.
The percentage of subjects in the final dataset for popPK weighing >90 kg with Ctrough <0.67 µg/mL were 28.8% (181 out of 629).

13.4.7. Dose/Exposure-Response Analysis

13.4.7.1. Methods

The applicant used two complementary modeling approaches to characterize the exposure response relationships for efficacy in subjects with psoriasis: 1) the 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 concentration and area under concentration-time curve (AUC); and 2) the longitudinal modeling approach employing a mechanism-based indirect response (IDR) model to characterize the time-course of the IGA and PASI outcomes. A sequential exposure-response modeling approach was employed in the 2 approaches to link systemic guselkumab exposure to efficacy endpoints including IGA 0/1, IGA 0, PASI 75, PASI 90, and PASI 100.

The applicant used population pharmacokinetic model parameter estimates in the longitudinal analysis through a sequential modeling process, while in the landmark analysis, the individual predicted steady-state trough serum guselkumab concentrations (Css) and AUC (cumulative AUC at Week 16 [AUC0-W16] and average weekly steady-state AUC [AUCss]) from the popPK analysis were used as independent variables to link with efficacy responses. Two IGA responses, IGA score of cleared (0) or minimal (1) (IGA≤1) and IGA score of cleared (0) (IGA0), and three PASI responses, PASI 75, PASI 90, and PASI 100 (PASI 75/90/100) were analyzed as categorical efficacy endpoints.

Longitudinal exposure-response analysis

The applicant developed the longitudinal model with the intention of fitting mechanism-based structural models to the data for the prediction of PASI and IGA outcomes. The goal was to answer key pharmacologic questions such as the timing of drug-dependent onset of effect, the maximum drug effect (Emax) and the steady-state concentration that achieves 50% of the maximum effect (EC50). Predictions are used to evaluate the proposed dosage recommendation and whether any treatment individual was needed based on patient factors.

PASI Response Component

The applicant combined three endpoints PASI 75, PASI 90, and PASI 100 into one ordered categorical endpoint, PASI having 4 possible outcomes: Pc=0, if achieving PASI 100; Pc=1, if achieving PASI 90 but not PASI 100; Pc=2, if achieving PASI75 but not PASI90; and Pc=3, if not achieving PASI 75. The placebo effect was modeled empirically and drug effect was then evaluated.

The PASI responses were modelled using:

$$probit[prob(Pc \leq k)] = \alpha_{k,Pc} + L_{Pc}(t) \quad (1)$$

where $\alpha_{k,Pc}$ are intercepts, and $L_{Pc}(t) = f_p(t) + f_d(t)$ represents placebo and drug effect. For the purpose of stabilizing parameter estimation, $\alpha_{k,Pc}$ are re-parameterized as ($\alpha_{1,Pc}$, $d_{0,Pc}$, $d_{2,Pc}$) with $d_{0,Pc}$, $d_{2,Pc} > 0$ such that $\alpha_{0,Pc} = \alpha_{1,Pc} - d_{0,Pc}$, and $\alpha_{2,Pc} = \alpha_{1,Pc} + d_{2,Pc}$.

The placebo effect was modelled empirically as

$$f_p(t) = Emax\,[1 - exp(-r*t)] \quad (2)$$

where Emax is the maximum placebo effect and r is the rate of onset. The drug effect was modeled with

$$f_d(t) = DE\,[1 - R(t)] \quad (3)$$

where DE represents the maximal drug effect. The drug effect was assumed to be driven by a latent variable R(t) determined by the following:

$$dR(t)/dt = k_{in}\,(1 - C_p/(IC_{50}+C_p) - k_{out} \cdot R(t) \quad (4)$$

where Cp is the drug concentration, and kin, IC50, and kout are parameters in a Type I in the indirect response model. The further assumption was that R = 1 at baseline, i.e., R(0) = 1, yielding $k_{in} = k_{out}$.

IGA Score Component

The applicant modelled IGA scores similarly as the PASI response criteria using the following equation:

$$\phi^{-1}[prob(IGA \leq k)] = \alpha_{k,IGA} + L_{IGA}(t) \quad (5)$$

where $\alpha_{k,\ IGA}$ are intercepts, re-parameterized as ($\alpha_{1,\ IGA}$, $d_{0,\ IGA}$, $d_{2,\ IGA}$, $d_{3,\ IGA}$) with $d_{0,\ IGA}$, $d_{2,\ IGA}$ and $d_{3,\ IGA} > 0$ such that $\alpha_{0,\ IGA} = \alpha_{1,\ IGA} - d_{0,\ IGA}$, $\alpha_{2,\ IGA} = \alpha_{1,\ IGA} + d_{2,\ IGA}$, and $\alpha_{3,}$ IGA = $\alpha_{2,\ IGA} + d_{3,\ IGA}$. $L_{IGA}(t)$ represents placebo and drug effect and were modeled similarly as in equation 2-4 above.

The exposure-response model was simultaneously fit to the PASI response criteria and IGA scores. The final exposure-response model was combined with the population PK model to simulate the predicted dose-response (D-R) relationships for the PASI 75/90/100 and IGA0/1 response frequencies. For each dose level, 10,000 subjects were simulated along with 400 replicates. The NONMEM generated variance-covariance matrices were used to account for uncertainties in the population pharmacokinetic and exposure-response models. Log-transformation for the relevant parameters was used to ensure that they remain positive.

Landmark exposure response analysis

In this analysis, the applicant performed direct exposure correlation for IGA≤1, IGA0 and PASI 75/90/100 responses at Week 16 and Week 28 respectively. Logistic regression, a commonly used link function for categorical variables, was used in the landmark analysis.

IGA Response

The two IGA responses (IGA≤1 and IGA0) were simultaneously modeled by the applicant through re-parameterization of the variable to an ordered categorical variable IGAR, with 3 possible outcomes: IGAR = 0, if IGA=0; IGAR =1, if IGA=1; IGAR =2, if IGA≥2. The probability of achieving each IGAR response was modeled using a standard ordinal mixed-effect logistic regression.

PASI Response

PASI 75/90/100 responses were simultaneously modeled by combining the three endpoints into one ordered categorical variable, PASI, with 4 possible outcomes: PASI=0, if achieving PASI 100; PASI=1, if achieving PASI 90 but not PASI 100; PASI=2, if achieving PASI 75 but not PASI 90; and PASI=3, if not achieving PASI 75. In both IGA and PASI responses, the applicant used the Emax model to evaluate the drug effect as follows:

$$f_d = Emax \cdot Exposure/(Exposure + EC_{50}) \quad (6)$$

where Emax represents the maximum drug effect achievable and EC_{50} is the guselkumab exposure at half the maximal effect. The base models described above were used for covariate analysis. The applicant preformed a covariate search on the intercept (βk, clinical response in the absence of drug exposure), EC_{50}, and Emax. Covariate relationships were included

additively on intercept in logit scale or multiplicatively on $EC5_0$ and Emax as power models for continuous covariates or as conditional effects relative to the most common category for categorical covariates. The applicant used the stepwise covariate model (SCM) building tool of PsN (stepwise forward selection and backward elimination) was used for the covariate search. The inclusion or exclusion of a covariate was determined by the likelihood ratio test: forward addition at the 1% significance level (e.g., a decrease in OFV of at least 6.63 with 1 degree of freedom [df]) and backward elimination at the 0.1% level (e.g., an increase in OFV of 10.83 with 1 df).

Exposure-Safety Analysis

The applicant used two approaches in the exploratory safety analyses for guselkumab. First, selected safety events (including adverse events, serious adverse events, and adverse events leading to discontinuation, infections, and infections requiring antimicrobial treatment) were analyzed according to quartiles of the observed steady-state trough guselkumab concentration levels at Week 28. Second, the same safety parameters were evaluated by population PK model-predicted parameters of maximum serum guselkumab concentration through Week 28 (Cmax), average daily serum guselkumab concentration up to Week 28 (Cave), and cumulative area under the concentration time curve through Week 28 (AUC0-28week). In this analysis, the applicant used pooled data from studies PSO3001 and PSO3002.

13.4.7.2. Results

13.4.7.2.1. Longitudinal exposure response analysis

The applicant selected the joint model that has placebo and drug effect parameters shared among the PASI response criteria and IGA components. Body weight effect was evaluated on k_{out} and EC_{50} as follows:

$$K_{out,i} = (BWT/90)^{Wkout} \cdot k_{out}$$

$$EC_{50,i} = (BWT/90)^{Wec50} \cdot EC_{50,}$$

where subscript *i* indicates the parameter value for the ith subject, and BWT is baseline body weight.

The final parameter estimates are shown in Table 73 below and a visual predictive check is shown on Figure **37**. Similar trends were observed on the VPC for IGA scores

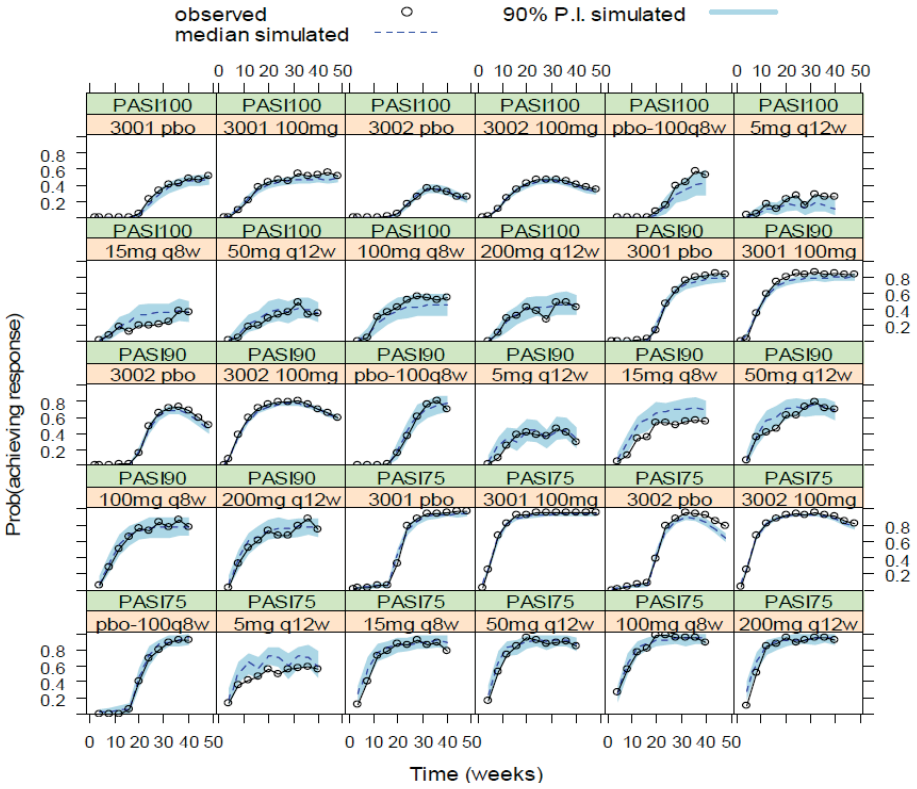
Table 73: Longitudinal exposure response model parameter estimates.

Parameter	$\alpha_{0,Pc}$	$d_{0,Pc}$	$d_{2,Pc}$	F_{max}	r (1/day)	k_{out} (1/day)	EC_{50} (μg/mL)	DE	ω^2
Effect Estimate(RSE)	-5.66 (1.54)	1.51 (1.36)	1.28 (1.68)	1.84 (4.09)	0.023 (7.03)	0.0212 (1.96)	0.038 (6.22)	5.35 (1.54)	1.92 (4.37)
Parameter	$\alpha_{0,IGA}$	$d_{0,IGA}$	$d_{2,IGA}$	$d_{3,IGA}$	S_L	W_{kout}	W_{ec50}		
Effect Estimate(RSE)	-3 (1.52)	1.61 (1.17)	1.33 (1.6)	2.17 (1.46)	0.669 (1.39)	1.41 (16.3)	-0.412 (12)		

Key: RSE, relative standard error; $\alpha_{0,Pc}$, intercept for PASI 90; $d_{0,Pc}$, difference between intercepts of PASI 100 and PASI 90; $d_{2,Pc}$, difference between intercepts of PASI 90 and PASI 75; F_{max}, maximum placebo effect; r, rate of placebo effect onset; k_{out}, disease amelioration rate; EC_{50}, potency; DE, maximum drug effect; ω^2, variance of between-subject variability; $\alpha_{0,IGA}$, intercept for IGA≤1; $d_{0,IGA}$, difference between intercepts of IGA≤1 and IGA=0; $d_{2,IGA}$, difference between intercepts of IGA≤2 and IGA≤1; $d_{3,IGA}$, difference between intercepts of IGA≤3 and IGA≤2; S_L, scale parameter; W_{kout}, baseline body weight effect on k_{out}; W_{ec50}, baseline body weight effect on EC_{50};

Source: Applicant's modelling simulation analysis, Table 6, page 28)

Figure 37**:** Observed (open circles) and predicted median (dash blue line) PASI 75/90/100 response rates plotted over time at various administered guselkumab doses over time determined according to bins of the model predicted guselkumab exposure metrics**.**

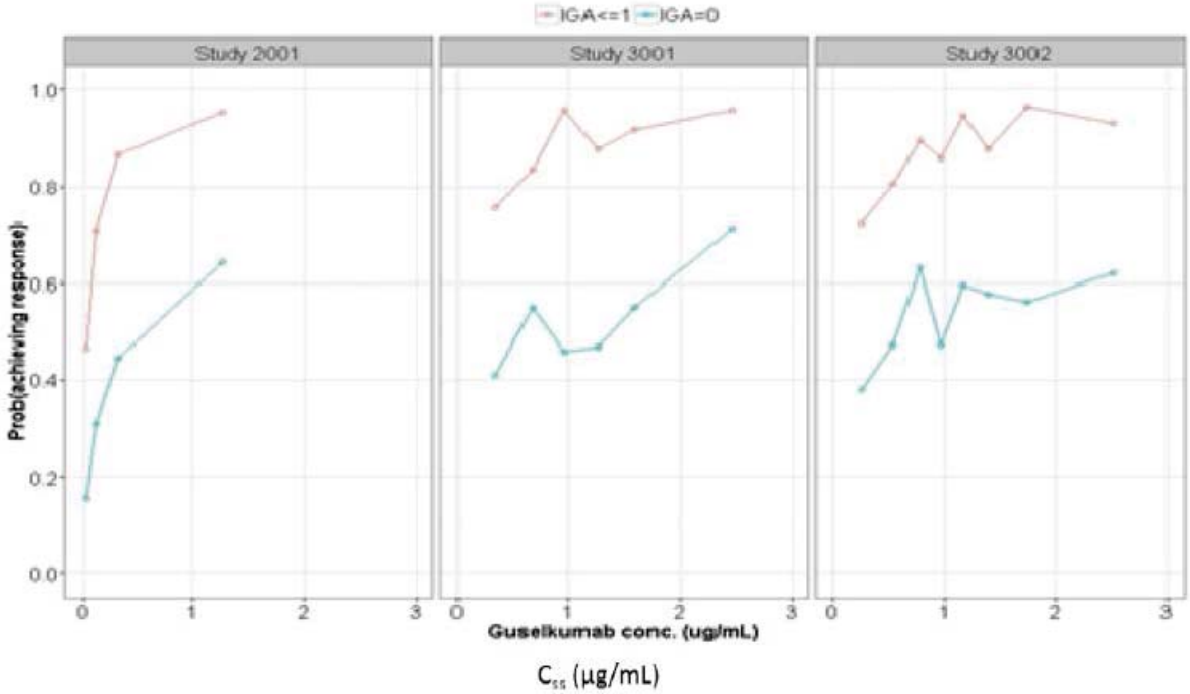


Key: The blue solid lines and the shaded areas are the simulated median responses and 90% prediction intervals (PI). PASI75/90/100=75%, 90% and 100% improvement in PASI relative to baseline; PI= prediction interval. Source: Applicant's modelling simulation analysis, Figure 1, page 29

13.4.7.2.2. Landmark exposure response analysis

The applicant performed six landmark analyses for IGA and PASI responses at Week 16 (when the coprimary endpoints were evaluated) and Week 28 (when serum guselkumab concentrations achieved a steady state). At Week 16, ordered IGA and PASI categorical responses were correlated to population PK model predicted AUC (cumulative AUC at Week 16 [AUC0-W16]). Since Week 16 was not trough visit, the applicant did not evaluate the efficacy relationship based on trough concentrations for this visit. At Week 28, population PK model predicted individual steady-state trough serum guselkumab concentrations (Css) and average weekly steady-state AUC [AUCss]) were used to link with the ordered IGA and PASI efficacy responses. A plot of IGA≤1/IGA0 at Week 28 versus Css by study is shown in Figure 38.

Figure 38: Plot of IGA≤1/IGA0 Responses at Week 28 versus steady state trough concentration by study.



Key: Open circles are the observed response rates determined according to bins of the model predicted guselkumab exposure metrics and were plotted at the median exposure within each bin. Key: Css=steady state trough concentration; IGA≤1= IGA score of cleared (0) or minimal (1); IGA0= IGA score of cleared (0). Source: Applicant's modelling simulation analysis, Figure 5, page 33.

The final parameter estimates are shown in Table 74 below.

Table 74: Parameter Estimates of Final Landmark ER Models

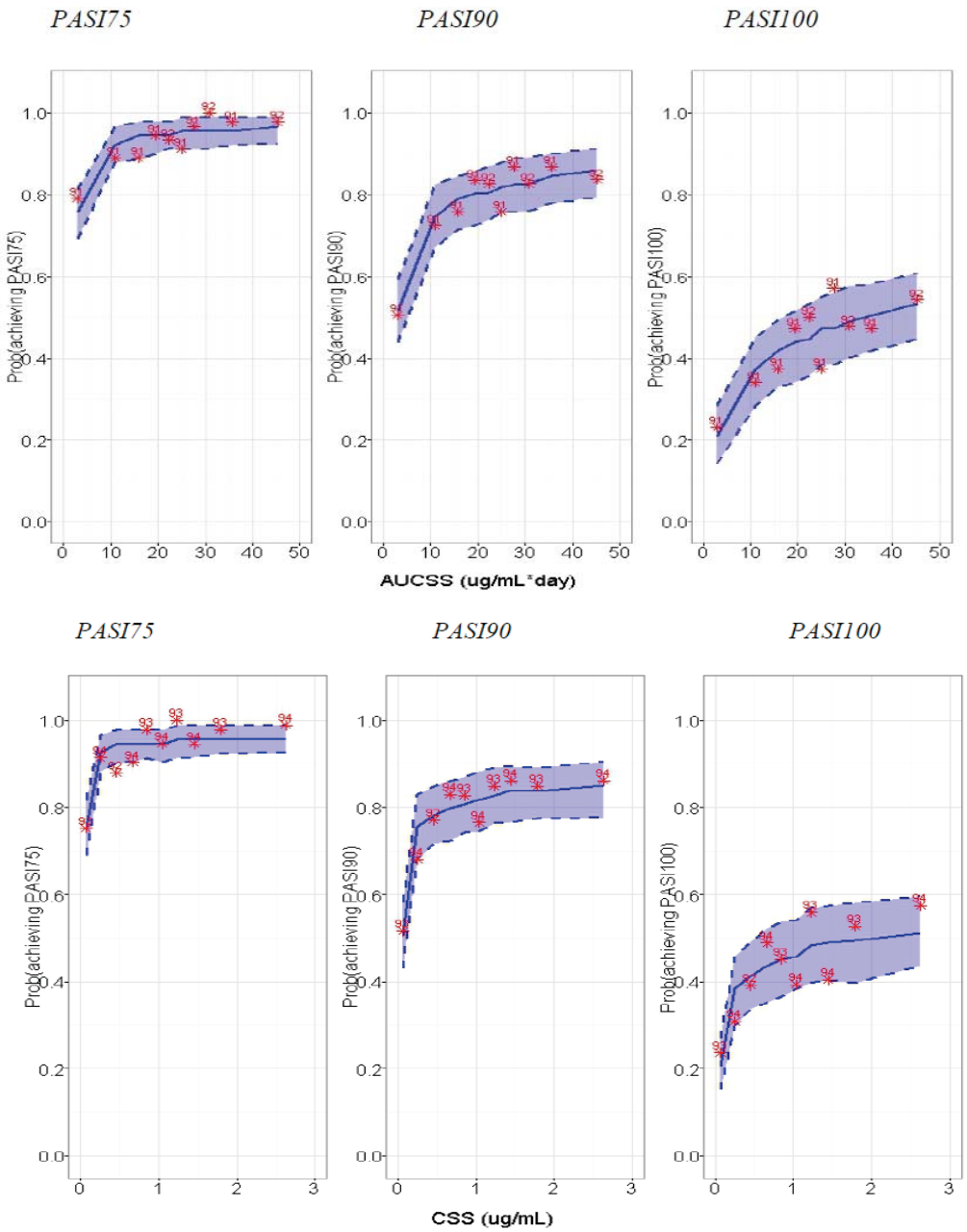
Parameters	Week 16 using AUC_{0-W16}[a]	Week 28 using AUC_{ss}[a]	Week 28 using C_{ss}[a]
IGA Categorical Modeling			
Run#	2	203	303
β_1	-2.47 (0.0704)	-3.90 (0.644)	-3.22 (0.553)
BWT on β_1	-1.19 (0.213)	-0.871 (0.341)	-0.883 (0.330)
d_0	2.12 (0.0439)	1.92 (0.0518)	1.94 (0.0509)
E_{max}	4.69 (0.0441)	6.22 (0.394)	5.46 (0.319)
EC_{50}	28.1 (0.252)	0.869 (0.703)	0.0212 (0.618)
BPASI on EC_{50}	---	1.44 (0.265)	1.75 (0.239)
PASI 75/90/100 Categorical Modeling			
Run#	102	502	402
β_1	-3.87 (0.0532)	-4.24 (0.554)	-3.20 (0.531)
BWT on β_1	-1.10 (0.216)	-0.937 (0.305)	-0.929 (0.306)
d_2	1.27 (0.0667)	1.46 (0.0863)	1.46 (0.0849)
d_0	1.55 (0.0471)	1.64 (0.0507)	1.66 (0.0498)
E_{max}	5.04 (0.0440)	5.93 (0.381)	4.82 (0.336)
EC_{50}	21.9 (0.257)	0.822 (0.827)	0.0220 (0.882)
DDUR on EC_{50}	---	0.699 (0.288)	0.976 (0.222)

[a]: *parameter estimate (RSE)*

Key: $\beta_0/\beta_1/\beta_2$=baseline response rate in logit scale where $\beta_0=\beta_1-d_0$ and $\beta_2=\beta_1+d_2$ (PASI modeling only); E_{max}=maximum drug effect in logit scale; EC_{50}= guselkumab exposure metrics to reach 50% maximum drug effect; BWT=baseline body weight; BPASI=baseline PASI; DDUR=disease duration; RSE = relative standard error; AUC_{0-W16}=cumulative AUC from time 0 to Week 16; AUC_{ss}=steady state weekly AUC; C_{ss}=steady state trough concentration; IGA= investigator's global assessment ; PASI= psoriasis area and severity index. *(Source: Applicant's modelling simulation analysis, Table 7, page 34).*

Figure 39 below shows the visual predictive check for the land mark ER model at week 28 (steady-state). Similar trends were observed for the IGA scores.

Figure 39: Visual Predictive Check (VPC) Plot of PASI75/90/100 at Week 28.

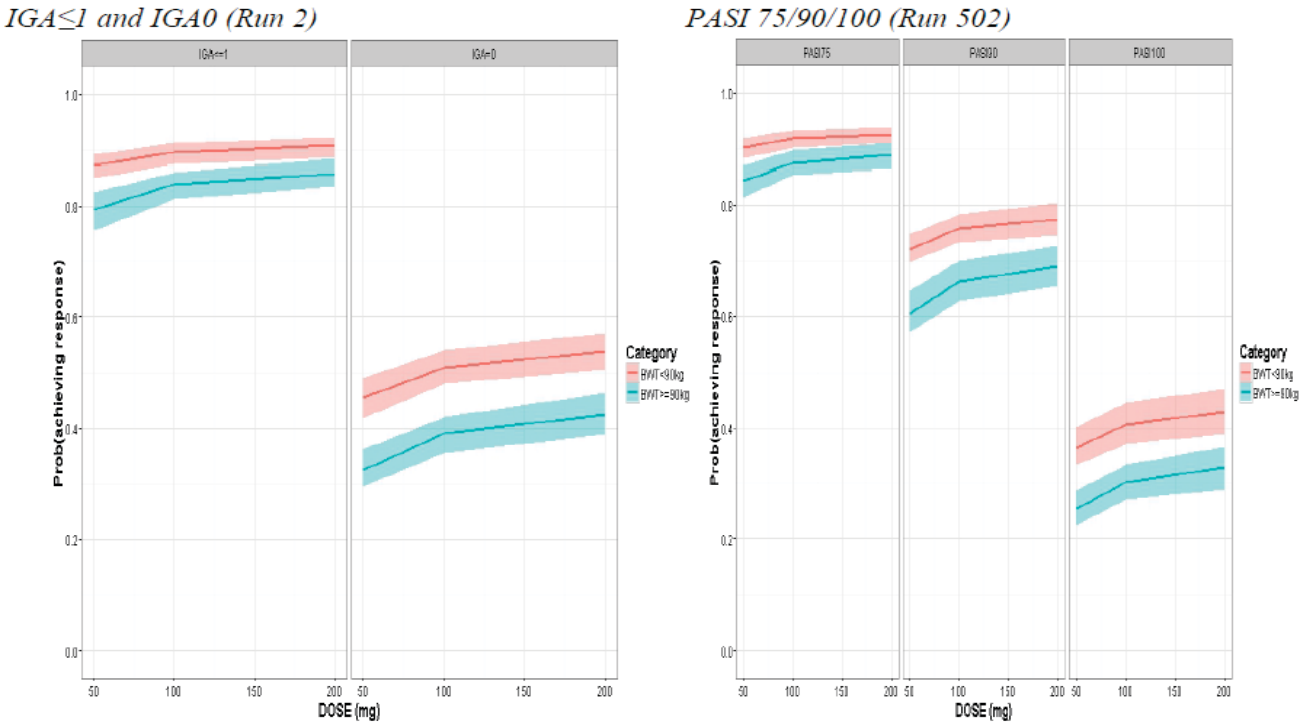


Key: The observed PASI 75/90/100 response rates (red asterisk) were determined according to bins of the model predicted guselkumab exposure metrics and were plotted at the median exposure within each bin. The red numbers are the numbers of subjects in each bin. The blue solid lines are the simulated median responses. The blue dotted lines and the shaded areas both represent the simulated 90% prediction intervals from 1000 replicates. Key: AUCss=steady state weekly AUC; Css=steady state trough concentration; PASI75/90/100=75%, 90% and 100% improvement in PASI relative to baseline. Source: Applicant's modelling simulation analysis, Figure 9, page 39.

Effect of body weight

The applicant performed simulations of IGA≤1, IGA0, and PASI 75/90/100 in subpopulations stratified by body weight (<90 kg or ≥90 kg). The simulated outcomes at Week 16 are shown in Figure 40. With the 100 mg q8w dose regimen, the model-predicted efficacy response rates in psoriatic subjects with a body weight ≥90 kg were lower than those in subjects <90 kg: approximately 9% to 12% lower for IGA0 and approximately 8% to 11% lower for PASI 100. Nevertheless, for subjects in both body weight categories, the guselkumab 100 mg q8w dose regimen is near the plateau of the dose-response curve.

Figure 40: Model predicted IGA≤1, IGA0 and PASI 75/90/100 response rates at Week 16 using AUC0-W16 as exposure parameter in subjects with body weight <90kg and ≥90kg.



Key: Solid lines and shaded area represent the model-predicted median response and 90% confidence intervals (CI), respectively, from 200 replicates. Key: BWT=baseline body weight; AUC0-W16=cumulative AUC from time 0 to week 16; IGA≤1= IGA score of cleared (0) or minimal (1); IGA0= IGA score of cleared (0); PASI75/90/100=75%, 90% and 100% improvement in PASI relative to baseline. Source: Applicant's modelling simulation analysis, Figure 16, page 51.

13.4.7.2.3. Exposure-safety analysis

The safety results of Guselkumab were evaluated in Phase 2 after subcutaneous doses ranging from 5 to 200 mg. The numbers of treated subjects with SAE through Week 16 were reasonable low and were comparable to adalimumab group as shown in Table 75. Generally, guselkumab was well tolerated across different doses evaluated. From Week 16 through Week 52, there were 5 more subjects who experienced at least 1 SAE (1 subject in the adalimumab group experienced multiple SAEs, 2 subjects in the 5 mg q12w guselkumab and 2 subjects in the 100 mg q8w guselkumab arm group).

Table 75: Number of subjects with 1 or more serious treatment-emergent adverse events through week 16

			CNTO 1959					
	Adalimumab	Placebo	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined
Subjects treated	43	42	41	41	42	42	41	207
Avg duration of follow-up (weeks)	16.29	15.67	16.10	16.45	16.50	16.07	15.94	16.22
Avg exposure (number of administrations)	6.72	2.90	3.00	3.00	2.98	2.98	2.98	2.99
Subjects with 1 or more serious adverse events	1 (2.3%)	1 (2.4%)	0	0	3 (7.1%)	0	0	3 (1.4%)
System-organ class/preferred term								
Infections and infestations	0	0	0	0	2 (4.8%)	0	0	2 (1.0%)
Appendicitis	0	0	0	0	1 (2.4%)	0	0	1 (0.5%)
Lung abscess	0	0	0	0	1 (2.4%)	0	0	1 (0.5%)
Gastrointestinal disorders	0	0	0	0	1 (2.4%)	0	0	1 (0.5%)
Umbilical hernia	0	0	0	0	1 (2.4%)	0	0	1 (0.5%)
Cardiac disorders	1 (2.3%)	0	0	0	0	0	0	0
Atrial flutter	1 (2.3%)	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	1 (2.4%)	0	0	0	0	0	0
Uterine prolapse	0	1 (2.4%)	0	0	0	0	0	0
Vascular disorders	1 (2.3%)	0	0	0	0	0	0	0
Haematoma	1 (2.3%)	0	0	0	0	0	0	0

(Source: Applicant's modelling simulation analysis, Figure 16, page 51).

Using pooled data from 2 Phase 3 (from the PSO3001 and PSO3002) studies, the applicant performed exposure-response analyses for safety using the following 2 approaches:

- the safety parameters of interest (AEs, SAEs, infections, infections requiring treatment and AEs leading to study agent discontinuation) were evaluated by Week 28 trough guselkumab concentrations at Week 28
- the same safety parameters were evaluated by the model predicted PK parameters through Week 28 (Cmax, average daily serum guselkumab concentration during drug exposure period [Cave], and AUC0-W28)

Data through Week 28 for the initial guselkumab group was used since the study designs with respect to the initial guselkumab were identical between these 2 studies. Only 3 serious infections were reported through Week 28 for the initial guselkumab group. In the analysis the applicant did not include serious infections. 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. All of the data from PSO3001 and PSO3002 for those subjects randomized to guselkumab at Week 0 who were treated with guselkumab and had serum guselkumab concentration data available at Week 28 were utilized for analysis.

The steady-state trough serum guselkumab concentrations at Week 28 were divided into 4 groups with approximately equal number of subjects in each group:

- First quartile: <0.61 µg/mL
- Second quartile: ≥0.61 µg/mL to <1.04 µg/mL
- Third quartile: ≥1.04 µg/mL to <1.54 µg/mL
- Fourth quartile: ≥1.54 µg/mL

While the exposure-response analyses of safety events showed that an increase in exposure to guselkumab appeared to be associated with a slightly higher frequency of infections, the significance of this finding is not clear due to the narrow range of guselkumab exposures analyzed in the Phase 3 studies. The applicant performed post-hoc multivariate logistic regression and concluded there was no evidence of exposure-safety concerns. Table 76 below shows the summary of treatment-emergent safety events

Table 76: Summary of Treatment-Emergent Adverse Events, Serious Adverse Events, Infections, Infections Requiring Oral or Parenteral Antimicrobial Treatment, or Adverse Events Leading to Study Agent Discontinuation Through Week 28 by Quartile of Serum Guselkumab

	Guselkumab Concentration Quartile			
	< 1st Quartile	≥ 1st Quartile to < 2nd Quartile	≥ 2nd Quartile to < 3rd Quartile	≥ 3rd Quartile
Analysis set: Subjects treated	179	182	180	182
Avg duration of follow-up (weeks)	28.52	28.35	28.25	28.19
Avg exposure (number of administrations)	17.76	17.75	17.69	17.68
Subjects with 1 or more adverse events	102 (57.0%)	116 (63.7%)	104 (57.8%)	121 (66.5%)
Subjects with 1 or more serious adverse events	8 (4.5%)	6 (3.3%)	3 (1.7%)	3 (1.6%)
Subjects with 1 or more infections	57 (31.8%)	59 (32.4%)	55 (30.6%)	80 (44.0%)
Subjects with 1 or more infections requiring treatment	19 (10.6%)	20 (11.0%)	16 (8.9%)	24 (13.2%)
Subjects who discontinued study agent because of adverse events	1 (0.6%)	1 (0.5%)	0	1 (0.5%)

Note: 1st quartile = 0.61 µg/mL, 2nd quartile = 1.04 µg/mL, 3rd quartile = 1.54 µg/mL are based on subjects in the guselkumab 100 mg group.

(Source: Applicant's Summary of Clinical Pharmacology, Table 18, page 81)

Reviewer's comments:

1. *Longitudinal and landmark analyses were conducted for IGA≤1, IGA0 and PASI75/90/100 responses using pooled data from two Phase 3 studies and one Phase 2 dose ranging study. The models adequately described the observed data. The simulation predictions from both models were generally consistent. Even though higher body weight was identified to be associated with slower onset and less sensitivity to treatment in the longitudinal model, dose adjustment based on body weight is not predicted to substantially improve response given*

that 100 mg q8w gave near maximum efficacy. One suggestion for improving the applicant's models could be to use responses as a continuous measure. However, this approach may not achieve much given the proposed models adequately described the data based on the presented visual predictive checks, even when stratified by body weight

2. *No consistent pattern was observed between guselkumab exposures and the rates of occurrence of SAEs, or AEs leading to discontinuation based on data from both Phase 2 and Phase 3 studies. Based upon data from Phase 3 studies, subjects with higher systemic guselkumab exposure (i.e., 4th quartile) for the proposed dose regimen of guselkumab (100 mg at Weeks 0, 4 and q8w thereafter) showed higher rates of adverse evets (7%) and more infections requiring treatment (8%) than those in the 3rd quartiles. Paradoxically, the 2nd quartile showed a higher event rate than 3rd quartile. Generally, guselkumab (100 mg at Weeks 0, 4 and q8w thereafter) was well-tolerated.*

13.5. Nonclinical Pharmacology/Toxicology

Clean version of the recommended labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
TRADENAME is an interleukin-23 blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available data on TRADENAME use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, TRADENAME may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 30 times the maximum recommended human dose (MRHD). Neonatal deaths were observed at 6- to 30-times the MRHD (see Data). The clinical significance of these nonclinical findings is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation
Risk Summary
There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need

Reference ID: 4123785

for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TRADENAME.

No effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 25 mg/kg twice weekly (15 times the MRHD based on a mg/kg comparison).

No effects on fertility parameters were observed after female guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly (60 times the MRHD based on a mg/kg comparison).

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/s/

MATTHEW E WHITE
07/13/2017

KENDALL A MARCUS
07/13/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

BLA:	761061
Drug Name:	TREMFYA (guselkumab) injection
Indication(s):	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant:	Janssen Biotech, Inc.
Date(s):	Letter Date: November 16, 2016
	PDUFA Date: July 17, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Matthew Guerra, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	Melinda McCord, M.D. / Kevin Clark, M.D. / Gordana Diglisic, M.D.
Project Manager:	Matthew White

Summary:

This memo closes the BLA assignment in DARRTS for the statistics team. The statistical review is complete and was included in the Multi-disciplinary Review and Evaluation, which was signed into DARRTS on July 13, 2017. The statistical analysis of the efficacy findings supports approval. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MATTHEW W GUERRA
07/14/2017

MOHAMED A ALOSH
07/14/2017

MEMORANDUM

Date: June19, 2017
To: BLA 761061
Regulatory Pathway: 351(a) of the Public Health Service Act
From: Gordana Diglisic, M.D., CDTL DDDP
Re: CDTL Review for BLA 761061

SUBJECT:

Submission type: Original BLA
Submission date: 11-16-2016
Drug: TREMFYA (guselkumab) injection, for subcutaneous use
Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Route: Subcutaneous injection
Applicant: Janssen Biotech, Inc.

Janssen Biotech, Inc. submitted a Biologics License Application (BLA) dated November 16, 2016 under section 351(a) of the Public Health Service Act for TREMFYA (guselkumab) injection, for subcutaneous use. TREMFYA is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23), and inhibits its interaction with the IL-23 receptor. TREMFYA is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The dosing regimen is 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. The proposed commercial presentation for guselkumab drug product (100 mg/mL) is a single-use pre-filled syringe (PFS) with a 1.0 mL fill volume.

This reviewer recommends approval of TREMFYA (guselkumab) injection, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The cross-discipline team leader (CDTL) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for the details.

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/s/

GORDANA DIGLISIC
06/19/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: June 13, 2017
To: BLA 761061
Regulatory Pathway: 351(a) of the Public Health Service Act
From: Melinda McCord, M.D., Medical Officer DDDP
Kevin Clark, M.D., Medical Officer DDDP
THROUGH: Gordana Diglisic, M.D., Clinical Team Leader DDDP
SUBJECT:
Submission type: Original BLA
Submission date: 11-16-2016
Drug: Guselkumab injection
Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Route: Subcutaneous injection
Applicant: Janssen Biotech, Inc.

Background
Janssen Biotech, Inc. submitted a Biologics License Application (BLA) dated November 16, 2016 under section 351(a) of the Public Health Service Act for TREMFYA (guselkumab) injection, for subcutaneous use. TREMFYA is an interleukin-23 blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The dosing regimen is 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter.

The applicant submitted data from two adequate and well-controlled trials [Trial 3001 (VOYAGE1) and Trial 3002 (VOYAGE2)], which provided evidence of the effectiveness of guselkumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. In addition, the applicant conducted a comprehensive assessment of the safety of guselkumab in the target population. The size of the safety database and the safety evaluations were sufficient to characterize the local and systemic treatment-emergent adverse reactions. The applicant established the benefit of guselkumab for the proposed indication. Approval is supported by the data included in this submission.

Recommendation:
The clinical team recommends approval of TREMFYA (guselkumab) injection, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Reference ID: 4113232

The clinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for the details.

Reference ID: 4113232

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/s/

MELINDA L MCCORD
06/19/2017

KEVIN L CLARK
06/19/2017

GORDANA DIGLISIC
06/19/2017

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Memorandum

FROM:	Karen A. Hicks, M.D., Medical Officer Division of Cardiovascular and Renal Products
THROUGH:	Norman L. Stockbridge, M.D., Ph.D., Director Division of Cardiovascular and Renal Products
TO:	Matthew White, RPM Division of Dermatology and Dental Products Kevin Clark, M.D., Medical Officer Division of Dermatology and Dental Products Melinda McCord, M.D., Medical Officer Division of Dermatology and Dental Products Gordana Diglisic, M.D., Team Leader Division of Dermatology and Dental Products
SUBJECT:	BLA 761061 (Guselkumab)
DATE RECEIVED:	December 13, 2016
DATE COMPLETED:	April 14, 2017

Reference ID: 4084700

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1. Executive Summary

Guselkumab (CNTO 1959) is an interleukin-23 blocker that is being developed for the treatment of adult patients with moderate-to-severe plaque psoriasis. Guselkumab, a human monoclonal IgG1λ antibody, binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor, thereby inhibiting the release of proinflammatory cytokines and chemokines. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

On November 16, 2016, the Division of Dermatology and Dental Products (DDDP) received a Biologics License Application (BLA 761061) from Janssen Biotech, Inc. (JBI) to support the proposed indication "for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy." The proposed dosing regimen is 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. This BLA has been approved for priority review under a tropical disease voucher. The Division of Dermatology and Dental Products (DDDP) has requested input from the Division of Cardiovascular and Renal Products (DCARP) on the cardiovascular (CV) findings and proposed labeling.

Given epidemiologic associations between psoriasis and CV events, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the applicant conducted additional analyses on CV events. The Clinical Events Committee (CEC) adjudicated potential CV events in four studies, including one phase 2 study (PSO2001) and three phase 3 studies (PSO3001, PSO3002, and PSO3003), as summarized below:

Study	Title
CNTO1959PSO2001 (2001)	"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 (X-PLORE)"
CNTO1959PSO3001 (3001)	"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 (VOYAGE 1)"
CNTO1959PSO3002 (3002)	"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)"

Reference ID: 4084700

Study	Title
CNTO1959PSO3003 (3003)	"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 (NAVIGATE)"
CNTO 1959: guselkumab	

Major adverse cardiovascular events (MACE) were defined as a composite of CV death, nonfatal MI, and nonfatal stroke. "Other CV events" included hospitalization for unstable angina (HUA); transient ischemic attack (TIA), venous thromboembolic (VTE) event; peripheral arterial thrombotic event; coronary revascularization (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery); heart failure (HF); arrhythmia requiring intervention, CV-related syncope; and severe/accelerated hypertension leading to hospitalization. The CEC also adjudicated all fatal events and classified these events as CV or Non-CV.

Below, we discuss the CV safety findings as they relate to each of the following outcomes/endpoints:

1) Major Adverse Cardiovascular Events and All-Cause Mortality
2) Other CV Events

These analyses are based on data through Week 48 for Studies 3001 and 3002, data through Week 40 for Study 3003, and entire trial data for Study 2001. These analyses also include the CEC-adjudicated CV events as well as 2 additional MACE events (ischemic stroke, ST-segment elevation MI) in the guselkumab treatment group identified by DCARP during the consultative review.

1) Major Adverse Cardiovascular Events and All-Cause Mortality

As previously noted, MACE was defined as a composite that included CV death, nonfatal MI, and nonfatal stroke. In studies 2001, 3001, 3002, and 3003 combined, there were a total of 15 MACE events, including

- 1 CV death due to MI (one subject in the guselkumab 5 mg q 12 weeks [q12w] treatment group);
- 12 MIs (5 subjects in the guselkumab, 2 subjects in the ustekinumab to guselkumab [randomized], 1 subject in the placebo to guselkumab, 1 subject in the European Union [EU]-approved adalimumab, 1 subject in the US-licensed adalimumab, and 2 subjects in the ustekinumab [1 randomized and 1 non-randomized] treatment groups; and
- 2 ischemic strokes (1 subject in the guselkumab and 1 subject in the non-randomized ustekinumab treatment groups).

Reference ID: 4084700

There were no MACE events in the placebo group. In the 4 studies combined, the annualized MACE rate was 0.84/100 subject-years (subj-yrs), 0.63/100 subj-yrs, 0.33/100 subj-yrs, and 5.08 subj-yrs in the guselkumab, US-licensed adalimumab, EU-approved adalimumab, and ustekinumab treatment groups, respectively.

Eight out of a total of 12 MIs occurred in subjects receiving guselkumab. The imbalance in MIs was driven largely by findings in a single trial (study 3002), where 4 subjects in the guselkumab 100 mg treatment group experienced MIs compared to 1 subject receiving US-licensed adalimumab in the adalimumab to guselkumab 100 mg treatment group. Annualized MI (and MACE) rates were 1.10/100 subj-yrs, 0.69/100 subj-yrs, and 2.33/100 subj-yrs in the continuous guselkumab 100 mg, overall guselkumab 100 mg, and US-licensed adalimumab treatment groups, respectively. This difference may be a true treatment difference, the effect of other differences in these subgroups, or a statistical anomaly.

The CEC also adjudicated 2 non-CV deaths. One non-CV death was due to methicillin resistant staphylococcus aureus pneumonia in a subject treated with US-licensed adalimumab, and the other non-CV death was due to pancreatic carcinoma in a subject treated with open-label ustekinumab.

We discuss the MACE and all-cause mortality findings for each individual study below.

Study 2001

Study 2001 was a phase 2 multicenter, randomized, placebo-and active-comparator-controlled, dose-ranging trial in 293 subjects with moderate to severe plaque psoriasis for at least 6 months prior to the first administration of study drug. This trial did not evaluate the guselkumab dosing regimen that is currently being proposed by the applicant for approval (i.e., 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter). Median follow-up was 1 subject-year each in the adalimumab (US-licensed and EU-approved), placebo, “Combined Guselkumab,” and “All Guselkumab” treatment groups, respectively.

The “Combined Guselkumab” treatment group included guselkumab treatment groups. The “All Guselkumab” treatment group included guselkumab treatment groups as well as placebo subjects who crossed over to guselkumab treatment.

Through Week 52, there were a total of 3 MACE events, including 1 CV death due to MI, 1 MI, and 1 ischemic stroke. Two events (1 MI and 1 stroke) occurred in the guselkumab 100 mg q8w treatment group (MACE rate of 5/100 subject-years [subj-yrs]), compared to 1 event (CV death) in the guselkumab 5 mg q12w treatment group (MACE rate of 2.86/100 subj-yrs). The MACE rate for the “Combined Guselkumab” treatment group was 1.56/100 subj-yrs, compared to 1.37/100 subj-yrs for the “All Guselkumab” treatment group, and 0 for placebo. The CV death was the only death in the study.

Study 3001

Study 3001(VOYAGE 1) was a phase 3 multicenter, randomized, double-blind, placebo and active comparator-controlled trial in 837 subjects with plaque-type psoriasis with or without psoriatic arthritis (PsA) for at least 6 months prior to first study drug administration. Subjects were also required to have a psoriasis area and severity index (PASI) ≥ 12, investigator's global assessment (IGA) ≥ 3, and involved body surface area (BSA) ≥ 10% at screening and at baseline and to be a candidate for phototherapy or systemic treatment for psoriasis. Through Week 48, median follow-up was 0.3 subject-years in the placebo treatment group, 0.6 subject-years in the placebo to guselkumab 100 mg treatment group, and 0.9 subject-years each in the guselkumab 100 mg, US-licensed adalimumab, and EU-approved adalimumab treatment groups, respectively.

Through Week 48, there were a total of 2 MACE events, including 1 MI in the EU-licensed adalimumab treatment group and 1 MI in the guselkumab 100 mg treatment group. The MACE rate was 0.52/100 subj-yrs for the EU-licensed adalimumab treatment group, compared to 0.34/100 subj-yrs for the guselkumab 100 mg treatment group, 0.25/100 sub-yrs for the "All Guselkumab" treatment group, and 0 for placebo.

There was also 1 non-CV death due to methicillin resistant staphylococcus aureus pneumonia in the US-approved adalimumab treatment group.

Study 3002

Study 3002 (VOYAGE 2) was a phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study in 993 subjects with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months prior to first study drug administration. Subjects were also required to have a PASI ≥ 12, IGA ≥ 3, and involved BSA ≥ 10% at screening and baseline and to be a candidate for phototherapy or systemic treatment for psoriasis. Through Week 48, the median follow-up was 0.3 subject-years for placebo, 0.9 subject-years for "Continuous Guselkumab 100 mg," 0.6 subject-years for "Overall Guselkumab 100 mg," 0.5 subject-years for US-licensed adalimumab, and 0.5 subject-years for EU-approved adalimumab.

Through Week 48, there were a total of 5 MACE events, including 1 MI in the placebo to guselkumab treatment group, 3 MIs in the guselkumab treatment group and 1 MI in the US-licensed adalimumab to guselkumab treatment group while the subject was receiving adalimumab. Of the 4 MIs in subjects receiving guselkumab, 1 MI occurred 162 days following the withdrawal of guselkumab (in the placebo to guselkumab treatment group) and the other 3 MIs occurred 8 to 52 days after receiving guselkumab.

The MACE (MI) rate was 1.37/100 subj-yrs in the placebo to guselkumab treatment group, 0.68/100 subj-yrs in the guselkumab treatment group, and 1.14/100 subj-yrs in the adalimumab to guselkumab treatment group.

There were no deaths.

Study 3003

Study 3003 was a phase 3 multicenter, randomized, double-blind trial in 872 subjects with moderate to severe plaque-type psoriasis (with or without PsA) for at least 6 months prior to first study drug administration. Subjects were also required to have an IGA ≥ 3, PASI score ≥ 12, involved BSA ≥ 10%, and be a candidate for either systemic therapy or phototherapy for psoriasis. Through Week 40, the median subject-years of follow-up were 0.5 each in the guselkumab treatment group and ustekinumab treatment group.

From Weeks 16 through 40, there were a total of 3 MACE events in the randomized treatment arms, including 2 MIs (1.48%) in the guselkumab treatment group and 1 MI (0.75%) in the ustekinumab treatment group. The annualized MACE rate was 3.23/100 subj-years for the guselkumab treatment group and 3.39/100 subj-years for the ustekinumab treatment groups. There were no deaths.

From Weeks 16 through 40 in the nonrandomized ustekinumab treatment group, there were 2 MACE events (1 MI and 1 stroke). The annualized MACE rate was 0.74/100 subj-years. There was also 1 non-CV death (0.37/100 subj-years) due to metastatic pancreatic carcinoma.

From Weeks 0 to 16, there were no MACE events in the enrolled and treated ustekinumab treatment group. There were no non-CV deaths.

2) Other CV Events

As previously noted, “Other CV Events” included HUA; TIA, VTE event, peripheral arterial thrombotic event; coronary revascularization (PCI and CABG surgery); HF; arrhythmia requiring intervention, CV-related syncope; and severe/accelerated hypertension (HTN) leading to hospitalization.

The CEC adjudicated a total of 15 “Other CV Events” in Studies 2001, 3001, 3002, and 3003 combined, including 7 arrhythmias requiring intervention, 4 HF events, 2 HUAs, 1 VTE, and 1 coronary revascularization, as follows:

- 2 hospitalizations for unstable angina (2 subjects in the guselkumab 100 mg treatment group)
- 1 venous thromboembolic event (1 subject in the EU-approved adalimumab treatment group)
- 1 coronary revascularization (PCI) (1 subject in the EU-approved adalimumab treatment group)

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- 4 heart failure events
  - 2 subjects in the EU-approved adalimumab treatment group
  - 1 subject in the US-licensed adalimumab treatment group
  - 1 subject in the guselkumab treatment group

- 7 arrhythmias requiring intervention
  - 2 events of atrial flutter in 1 subject in the US-licensed adalimumab treatment group
  - 1 subject in the placebo to guselkumab 100 mg treatment group (sinus node dysfunction requiring permanent pacemaker placement)
  - 1 subject in the randomized ustekinumab to guselkumab 100 mg treatment group while receiving guselkumab (sinus bradycardia due to nebivolol)
  - 1 subject in the non-randomized ustekinumab treatment group (weeks 16 to 40) (supraventricular tachycardia)
  - 2 subjects in the ustekinumab treatment group through week 16 (atrial fibrillation)

We note that US prescribing information for HUMIRA (adalimumab) includes heart failure under Section 5, Warnings and Precautions. We also note that the following less common adverse reactions are reported: arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, and tachycardia.

There were no “Other CV Events” in the placebo group. For Studies 2001, 3001, 3002, and 3003 combined, the annualized rate for “Other CV Events” was 0.42, 1.89, 1.33, and 5.08 in the guselkumab, US-licensed adalimumb, EU-approved adalimumab, and ustekinumab treatment groups, respectively.

We discuss the “Other CV Events” findings for each individual study below.

Study 2001

In Study 2001, there were a total of 2 (9.52%) “Other CV Events” (11.8/100 subj-years) in the US adalimumab treatment group. One subject experienced two events of arrhythmia requiring intervention (atrial flutter).

Study 3001

In Study 3001 through Week 48, there were a total of 4 (1.83%) “Other CV Events” (2.08/100 subj-years) in the EU-approved adalimumab treatment group including 1 VTE, 1 coronary revascularization (PCI), and 2 HF hospitalizations in a single subject with a history of a dilated cardiomyopathy. There was also 1 (0.61%) arrhythmia requiring intervention (sinus node dysfunction requiring pacemaker implantation for sick sinus syndrome) (1.0/100 subj-years) in the placebo to guselkumab 100 mg treatment group.

Study 3002
In Study 3002 through Week 48, there were a total of 3 “Other CV Events,” including 1 HUA event in the guselkumab treatment group, 1 heart failure hospitalization in the guselkumab treatment group, and 1 urgent heart failure visit in the US-licensed adalimumab treatment group. Rates for “Other CV Events” were 2.33/100 subj-yrs in the US-licensed adalimumab treatment group, 0.37/100 subj-yrs in the “Continuous Guselkumab” treatment group, and 0.34/100 subj-yrs in the “Overall Guselkumab” treatment group.

Study 3003
From Weeks 16 to 40, there were a total of 2 “Other CV Events” in the randomized treatment groups including 1 HUA and 1 arrhythmia requiring intervention (sinus bradycardia due to nebivolol) in the guselkumab treatment group (3.23/100 subj-yrs).

From Weeks 16 to 40, there was 1 “Other CV Event” in the non-randomized ustekinumab treatment group including an arrhythmia requiring intervention (supraventricular tachycardia) (0.37/100 subj-yrs). There was also 1 non CV death due to pancreatic carcinoma.

Through Week 16, there were 2 arrhythmias requiring intervention (atrial fibrillation) (0.74/100 subj-yrs).

Conclusion
In conclusion, there were a total of 15 MACE and 15 “Other CV Events” in studies 2001, 3001, 3002, and 3003 combined. There were no MACE or “Other CV Events” in the placebo treatment group. The annualized MACE rates for the 4 studies combined was 0.84/100 subject-years (subj-yrs), 0.63/100 subj-yrs, 0.33/100 subj-yrs, and 5.08 subj-yrs in the guselkumab, US-licensed adalimumab, EU-approved adalimumab, and ustekinumab treatment groups, respectively. Subjects experiencing MACE events generally had risk factors for CV disease. The annualized rates for “Other CV Events” for the 4 studies combined was 0.42/100 subj-yrs, 1.89/100 subj-yrs, 1.33/100 subj-yrs, and 5.08/100 subj-yrs in the guselkumab, US-licensed adalimumab, EU-approved adalimumab, and ustekinumab treatment groups, respectively.

Based on the available data, at this time we do not observe evidence of a clinically meaningful imbalance in MACE or “Other CV Events” with guselkumab.

We note that according to the Response to Information Request dated March 24, 2017, the applicant indicates that “adjudicated data from Week 48 through Week 160” of Studies 3001 and 3002 “are not yet available since database locks beyond Week 48 have not yet occurred. CV adjudication has been recently completed for data from Week 40 through Week 60 in the PSO3003 study; however, formal analyses of these data have not been completed.”

We also note that the 120-Day Safety Update submitted on March 16, 2017 indicates that there are additional MACE and "Other CV Events" that have occurred after database lock in Studies 3001, 3002, and 3003. These data are not currently available to us for review. DCARP recommends requesting these data from the sponsor when available to further evaluate the CV safety profile of guselkumab.

2. Responses to DDDP's Questions

DDDP requests your assistance with the following questions:

1. Is the difference in proportion of cardiac treatment emergent adverse events including hypertension (HTN) in the guselkumab group clinically significant?

   DCARP Response: Please see the issues we have summarized in the Executive Summary regarding MACE and "Other CV Events."

   With regard to hypertension, DCARP notes that according to DDDP, "no treatment related effects on blood pressure and electrocardiograms" were observed in the nonclinical studies. DCARP also notes that through Week 16 in Studies 3001 (VOYAGE 1) and 3002 (VOYAGE 2), the percentage of subjects reporting hypertension was 2.6% in the guselkumab treatment group at the proposed marketing dose (i.e. 100 mg at Week 1, Week 4, and every 8 weeks thereafter), 2.6% in the US-licensed adalimumab treatment group, and 1.9% in the placebo treatment group. DCARP does not find the difference in the proportion of treatment emergent adverse events for hypertension to be clinically significant.

   DCARP notes that adalimumab (HUMIRA), a tumor necrosis factor indicated for the treatment of plaque psoriasis, includes hypertension as an adverse reaction in Table 1 ("Adverse Reactions Reported by ≥ 5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled Rheumatoid Arthritis Studies (Studies RA-I, RA-II, RA-III, and RA-IV)" of its prescribing information. Hypertension was reported in 5% of subjects receiving treatment with HUMIRA 40 mg subcutaneous every other week compared to 3% of subjects receiving placebo.

   DCARP also notes that the applicant provided a response on February 17, 2017 to an Information Request from DDDP regarding hypertension. In the Clinical Study Reports for studies 3001 and 3002, there were no clinically meaningful changes from baseline in systolic and diastolic blood pressure at Week 16 and Week 48. A shift table analysis was conducted with data from the placebo-controlled period (Week 0 and Week 16) for these pooled studies and demonstrated that only 30% of subjects had a normal baseline value for systolic blood pressure (SBP) defined as ≥ 90 to ≤ 120 mm Hg, and only 50% of subjects had a normal baseline value for diastolic blood pressure, defined as ≥ 60 to ≤ 80 mm Hg. Approximately 70% of guselkumab, placebo, and adalimumab subjects had elevated systolic values at baseline and approximately 40% of these subjects had elevated diastolic values at

baseline. Approximately 35% of subjects in guselkumab, placebo, and adalimumab treatment groups experienced shifts from a normal baseline value to an elevated value at Week 16 for systolic blood pressure and 20% of these subjects experienced shifts from a normal baseline value to an elevated value at Week 16 for diastolic blood pressure.

Although the to-be-marketed dosing regimen was not evaluated in Study 2001, should DDDP have further concerns about hypertension, consider determining whether there were any dose-related increases in blood pressure with guselkumab from this phase 2 study.

2. Should this information be included in the labeling for Guselkumab?

   DCARP Response: No, there is no aspect of these findings—MACE or hypertension—that we would mention anywhere in labeling.

Additional Comments:

1. Most, but not all, potential CV events were referred appropriately to the CEC for adjudication. The following events should also have been referred:

   a. Study 2001:
      - Atrial Fibrillation (CNTO1959PSO2001-0103-00247) (Adalimumab)
      - Atrial Fibrillation (CNTO1959PS02001-0022-00193) (CNTO1959 100 mg (q8w)

      Reviewer Comments: The applicant was queried about these events. In the Response to Information Request dated April 5, 2017, the applicant indicated that only serious adverse events were submitted to the CEC for CV adjudication. Both of the atrial fibrillation events were reported as nonserious adverse events and were not submitted for CV adjudication.

      The applicant also indicated that the strategy for identifying trigger terms was different in Study 2001 (retrospective identification of trigger terms from final serious adverse event listing) compared with the Phase 3 studies (prospective identification of trigger terms from the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and standardised MedDRA queries (SMQs).

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b. Study 3001:
   - Atrial Fibrillation (CNTO1959PSO3001-DE00488-10063) (Guselkumab 100 mg)

   <u>Reviewer Comments</u>: The applicant was queried about this event. In the Response to Information Request dated April 5, 2017, the applicant indicated that there were no medical records available for this nonserious event; hence, "there was no CEC package to submit for adjudication."

2. DCARP identified 1 additional stroke and 1 additional MI. There is also one arrhythmia requiring intervention that is not likely an event. These cases are discussed in more detail below.

   a. Ischemic Stroke (CNTO1959PSO2001-0022-00193) (CNTO 1959 100 mg q8w): Initially, the CEC did not adjudicate this event as a stroke. Following DCARP's query to the sponsor, the CEC reviewed the event and according to the sponsor, "noted that an administrative error resulted in the wrong source documentation being associated with subject 00193. This event was re-adjudicated by the CEC to be an "ischemic stroke." The analyses in the sponsor's application do not include this event. DCARP has included this event in the analyses.

   b. ST segment elevation MI (STEMI) (Acute Myocardial Infarction) (CNTO1959PSO3002-US91507-20944) (Guselkumab). Initially, the CEC adjudicated this event as "Hospitalization for Unstable Angina." This event is a "STEMI" and not "Hospitalization for Unstable Angina." Although there are no cardiac biomarkers available, the source documents indicate that the subject underwent cardiac catheterization which revealed critical terminal left main, ostial left circumflex, and ostial left anterior descending coronary artery disease. During the procedure, the subject became hemodynamically unstable in the cardiac catheterization laboratory and developed ST segment elevation. An intraaortic balloon pump was placed, but according to the Cardiothoracic Surgeon's Operative note, the subject continued to have ST segment elevation. The patient was referred for emergency coronary artery bypass graft surgery.

   <u>Reviewer Comments</u>: According to the Response to Information Request dated April 5, 2017, the applicant indicates that the CEC adjudicated this event as "Hospitalization for Unstable Angina" because no cardiac biomarkers were available. Although the CEC "requested the applicant to obtain biomarker data from the investigative site," the site sent additional medical records on two occasions, "but these records did not include biomarker data, and the site confirmed that no cardiac enzyme laboratory tests were done during the entire admission." Although there are no cardiac biomarker results, the totality of the data indicates that this subject

experienced a ST-segment elevation MI. This event is included in DCARP analyses.

c. No Event (CNTO1959PSO3003-RU00371-30982) (Ustekinumab). Initially, the CEC adjudicated this event of atrial fibrillation as an "Arrhythmia Requiring Intervention." This subject's ECG demonstrated atrial fibrillation during screening and prior to the first dose of study drug. The CEC packet does not indicate that the subject was treated specifically for atrial fibrillation or that the underlying condition of atrial fibrillation worsened over the course of the trial, criteria that would need to be satisfied to adjudicate this event as an arrhythmia requiring intervention. Hence, I do not think that the preexisting atrial fibrillation satisfies the criteria for an event.

Reviewer Comments: The applicant was queried about this event. In the Response to Information Request dated April 6, 2017, the applicant agrees with the Agency that this was not a treatment emergent adverse event because the event occurred prior to the initiation of study drug. Hence, the applicant has not included this event as a treatment emergent adverse event in the safety analyses for Study 3003.

The applicant also indicated that for the analyses of adjudicated CV events, "event time is not collected by the CEC in the adjudication case report form for any endpoint. Therefore, only event date is used to determine treatment emergent status of adjudicated events, and based on the rules outlined [in the CEC Charter], this event was considered as treatment emergent."

Since the source documents indicated that the subject "received treatment," the CEC adjudicated this event as an arrhythmia requiring intervention, although it is unclear exactly what treatment the subject received and whether the treatment was specifically for atrial fibrillation.

3. Background

[redacted] (b) (4)) CEC adjudicated potential CV events in four studies, including one phase 2 study (PSO2001) and three phase 3 studies (PSO3001, PSO3002, and PSO3003), as summarized below:

Study	Title and Study Period
CNTO1959PSO2001 (2001)	"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 (X-PLORE)" **Study Period:** October 25, 2011 (first subject signed informed consent) – August 5, 2013 (last study visit for last subject at Week 52)
CNTO1959PSO3001 (3001)	"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 (VOYAGE 1)" **Study Period:** December 3, 2014 (first subject screened) – April 27, 2016 (Week 48 study visit for last subject)
CNTO1959PSO3002 (3002)	"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 Period:** November 3, 2014 (first subject screened) – May 19, 2016 (last study visit for last subject)
CNTO1959PSO3003 (3003)	"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 (NAVIGATE)" **Study Period:** October 7, 2014 (first subject screened) – December 25, 2015)
CNTO 1959: guselkumab	

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The CEC adjudicated the following potential CV events:

1. CV death (all fatal events were adjudicated for CV vs. Non-CV cause)
2. Non-fatal myocardial infarction (MI)
3. Non-fatal stroke
4. Hospitalization for Unstable Angina (HUA)
5. Transient Ischemic Attack (TIA)
6. Venous thromboembolic (VTE) event
7. Peripheral arterial thrombotic event
8. Coronary revascularization (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
9. Heart failure (HF)
10. Arrhythmia requiring intervention
11. Syncope (CV)
12. Severe/accelerated hypertension leading to hospitalization

DDDP has requested input from DCARP on the CV findings and proposed labeling.

4. Materials Reviewed

1. Selected Analysis and Raw Datasets

   \\CDSESUB1\EVSPROD\BLA761061\0000 (SDN 1, November 16, 2016)

2. Applicant's Responses to Selected Information Requests

   \\CDSESUB1\EVSPROD\BLA761061\0014 (SDN 15, February 17, 2017)
   \\CDSESUB1\EVSPROD\BLA761061\0020 (SDN 21, March 16, 2017)
   \\CDSESUB1\EVSPROD\BLA761061\0022 (SDN 23, March 24, 2017)
   \\CDSESUB1\EVSPROD\BLA761061\0029 (SDN 30, April 5, 2017)
   \\CDSESUB1\EVSPROD\BLA761061\0030 (SDN 31, April 6, 2017)

3. (b) (4)
   Clinical Events Committee (CEC) Charter (Version 1 dated December 14, 2015)
4. Selected Clinical Event Committee Packets, Case Report Forms (CRFs), and narratives
5. 120-Day Safety Update Report for BLA 761061 dated March 1, 2017 and submitted on March 16, 2017
6. Selected sections of the Clinical Study Report (CSR) for Protocol CNTO1959PSO2001 titled "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 (X-PLORE)"

Reference ID: 4084700

7. Selected sections of the 48-Week CSR for Protocol CNTO1959PSO3001 titled "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 (VOYAGE 1)"
8. Selected sections of the 48-Week CSR for Protocol CNTO1959PSO3002 titled "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)"
9. Selected sections of the 40-Week CSR for Protocol CNTO1959PSO3003 titled "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 (NAVIGATE)"
10. Edition 7 of the Investigator's Brochure dated January 4, 2017 and submitted to IND 105004 (SDN 223, January 18, 2017)

5. Review Strategy

According to the Response to Information Request dated March 24, 2017, the applicant indicates that "CV adjudication has been completed for all locked data (through Week 48) for both PSO3001 and PS03002; however, adjudicated data from Week 48 through Week 160 of these 2 studies are not available since database locks beyond Week 48 have not yet occurred. CV adjudication has been recently completed for data from Week 40 through Week 60 in the PSO3003 study; however, formal analyses of these data have not been completed." Hence, data through Week 48 for Studies 3001 and 3002, data through Week 40 for Study 3003, and entire trial data for Study 2001 were available for this consultative review.

DCARP notes that the 120-Day Safety Update submitted on March 16, 2017 includes additional events that have occurred after database lock in Studies 3001, 3002, and 3003 for which we do not have available data. These data have not been included in DCARP's analyses, but the events are summarized in Section 7.

Following a review of the CEC Charter, I reviewed selected CEC packets and Case Report Forms (CRFs) to assess the quality of the adjudication and to ensure that potential CV events were referred appropriately to the CEC for review. I also reviewed selected datasets for potential CV events. In addition, I reviewed selected sections of the protocols and clinical study reports for studies 2001, 3001, 3002, and 3003. In Section 6, I summarize MACE and "Other CV Events" results for all studies combined (Studies 2001, 3001, 3002, and 3003). In Section 7, I summarize the treatment groups and study designs for the individual studies."

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6. MACE and "Other CV Events" for All 4 Studies Combined

MACE rates and rates for "Other CV Events" are summarized in Table 1 for Studies 2001, 3001, 3002, and 3003 combined. The MACE rates for guselkumab, ustekinumab, US-licensed adalimumab, and EU-approved adalimumab are 0.84, 5.08, 0.63, and 0.33, respectively. There were no MACE events in the placebo group. Rates for "Other CV Events" were 0.42, 5.08, 1.89, and 1.33 in the guselkumab, ustekinumab, US-licensed adalimumab, and EU-approved adalimumab treatment groups, respectively. There were no "Other CV Events" in the placebo group.

Table 1. MACE and "Other CV Events" (Studies 2001, 3001, 3002, and 3003 Combined)

	Adalimumab (US)	Adalimumab (EU)	Guselkumab	Ustekinumab
# of subjects treated	217	407	1602	133
Total subject-years of follow-up	159	301	1191	59
MACE				
# of Events (%)	1 (0.46)	1 (0.25)	10 (0.62)	3 (2.26)
100 Subject-Years	0.63	0.33	0.84	5.08
Other CV Events				
# of Events (%)	3 (1.38)	4 (0.98)	5 (0.31)	3 (2.26)
100 Subject-Years	1.89	1.33	0.42	5.08
Analysis by Ruquan Liu, MD, MS				

Based on the available data, at this time we do not observe evidence of a clinically meaningful imbalance in MACE or "Other CV Events" with guselkumab.

7. Individual Studies - Study Design and Treatment Groups

7.1. Study 2001

Study 2001 was a phase 2 multicenter, randomized, placebo-and active-comparator-controlled, dose-ranging trial in subjects with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic treatment for psoriasis.

This trial did not evaluate the guselkumab dosing regimen that is currently being proposed by the applicant for approval (i.e., 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter).

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7.1.1. Key Inclusion Criteria:

1) Men or women ≥ 18 years of age
2) Diagnosis of plaque-type psoriasis with or without psoriatic arthritis for at least 6 months prior to first study drug administration
3) PASI ≥ 12, PGA ≥ 3, and involved BSA ≥ 10% at screening and baseline
4) Candidate for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment)
5) If a woman, postmenopausal or premenopausal and either surgically sterile or practicing a highly effective method of birth control
6) Met tuberculosis (TB) screening criteria

7.1.2. Key Exclusion Criteria:

1) Signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease
2) Unstable CV disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.
3) Known malignancy or history of malignancy
4) Chronic or recurrent infectious disease
5) Hospitalization in the past 3 months for asthma, previous intubation for the treatment of asthma, oral corticosteroids for the treatment of asthma, or more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within the previous 6 months
6) Transplanted organ
7) History of an infected joint prosthesis
8) Hospitalization or treatment with intravenous antibiotics for a serious infection (e.g., sepsis, pneumonia, or pyelonephritis) during the 2 months prior to screening
9) Contraindication to anti-TNFα therapy (e.g., history of, or concurrent HF including medically controlled asymptomatic HF)
10) Herpes zoster within the 2 months prior to screening
11) Woman who is pregnant, breastfeeding, or planning to become pregnant or man who plans to father a child while enrolled in the study or within 5 months after receiving the last administration of study drug
12) Prior systemic immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hyrdoxyurea, and tacrolimus) or anakinra within 4 weeks of the first administration of study drug
13) Prior phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation
14) Prior topical medications/treatments that could affect psoriasis or PGA evaluation
15) Prior anti-TNFα therapy other than adalimumab within 3 months or 5 half-lives of the first administration of study drug, whichever is longer

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16) Prior therapeutic agent directly targeted to IL-12, IL-17, or IL-23 (including but not limited to ustekinumab, briakinumab [ABT-874], AIN457, and SCH900222) within 6 months of the first administration of study drug
17) Prior natalizumab, efalizumab, or therapy with agents that modulate B cells or T cells (e.g., rituximab, alemtuzumab, abatacept, alefacept, or visilizumab) within 12 months of first study drug administration
18) Current lithium, antimalarial, or IM gold therapy or within 4 weeks of the first study drug administration
19) Prior experimental antibody or biologic therapy within the previous 6 months
20) Live virus or bacterial vaccination within 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to first study drug administration
21) Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening
22) Chest X-Ray within 3 months prior to fist study drug administration that shows an abnormality suggestive of a malignancy or current active infection, including TB
23) Latent or active granulomatous disease
24) Nontuberculous mycobacterial infection or opportunistic infection
25) Indeterminate initial and repeat QuantiFERON-TB Gold test results or a newly positive QuantiFERON-TB Gold test and unwilling or unable to undergo TB prophylaxis treatment
26) Human immunodeficiency virus (HIV) positive
27) Hepatitis B virus positive or has antibodies to hepatitis C virus
28) Substance abuse within the previous 12 months

7.1.3. Treatment Groups and Study Design

Study duration was approximately 56 weeks, including a

- Screening phase (Week -4 through Week 0)
- Treatment phase (with dosing from Week 0 through Week 40)
- Follow-Up phase (after Week 40 through Week 52)

Eligible subjects were randomized equally to 7 treatment groups, as summarized in Table 2. Figure 1 summarizes the study design. Database locks (DBL) were scheduled for Weeks 16, 40, and 52.

Reference ID: 4084700

Table 2. Treatment Regimen (Study 2001)

Group	Planned Number of subjects	Treatment
Group 1	40	Placebo SC administration at Weeks 0, 4, and 8 followed by CNTO 1959 100 mg SC administration at Week 16, and q8w thereafter through Week 40.
Group 2	40	CNTO 1959 5 mg SC administrations at Weeks 0, 4, and 16 followed by CNTO 1959 5 mg SC administration q12w thereafter through Week 40.
Group 3	40	CNTO 1959 15 mg SC administrations at Weeks 0, 8, and 16 followed by CNTO 1959 15 mg SC administration q8w thereafter through Week 40.
Group 4	40	CNTO 1959 50 mg SC administrations at Weeks 0, 4, and 16 followed by CNTO 1959 50 mg SC administration q12w thereafter through Week 40.
Group 5	40	CNTO 1959 100 mg SC administrations at Weeks 0, 8, and 16 followed by CNTO 1959 100 mg SC administration q8w thereafter through Week 40.
Group 6	40	CNTO 1959 200 mg SC administrations at Weeks 0, 4, and 16 followed by CNTO 1959 200 mg SC administration q12w thereafter through Week 40.
Group 7	40	Adalimumab 80 mg SC administration at Week 0 followed by 40 mg SC administration at Week 1 and every other week thereafter through Week 39.

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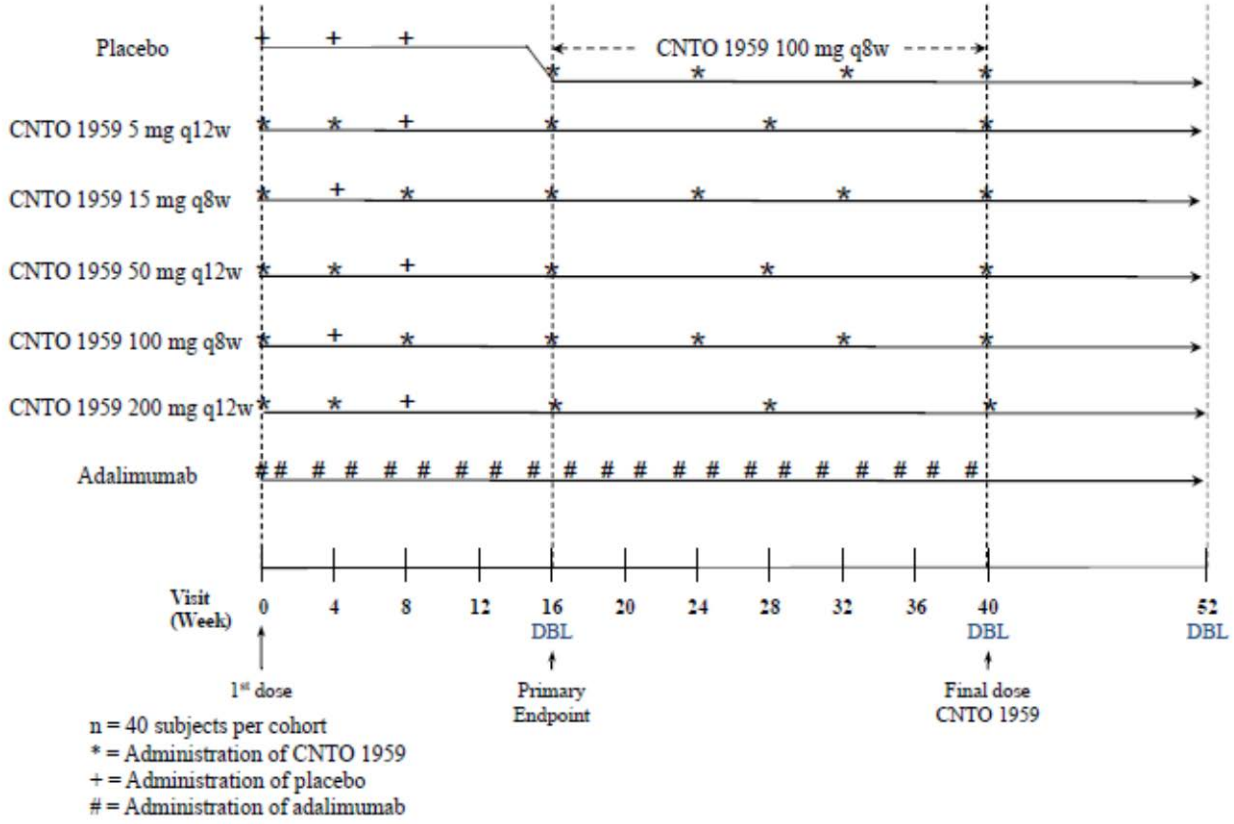
Figure 1. Study Design (Study 2001)



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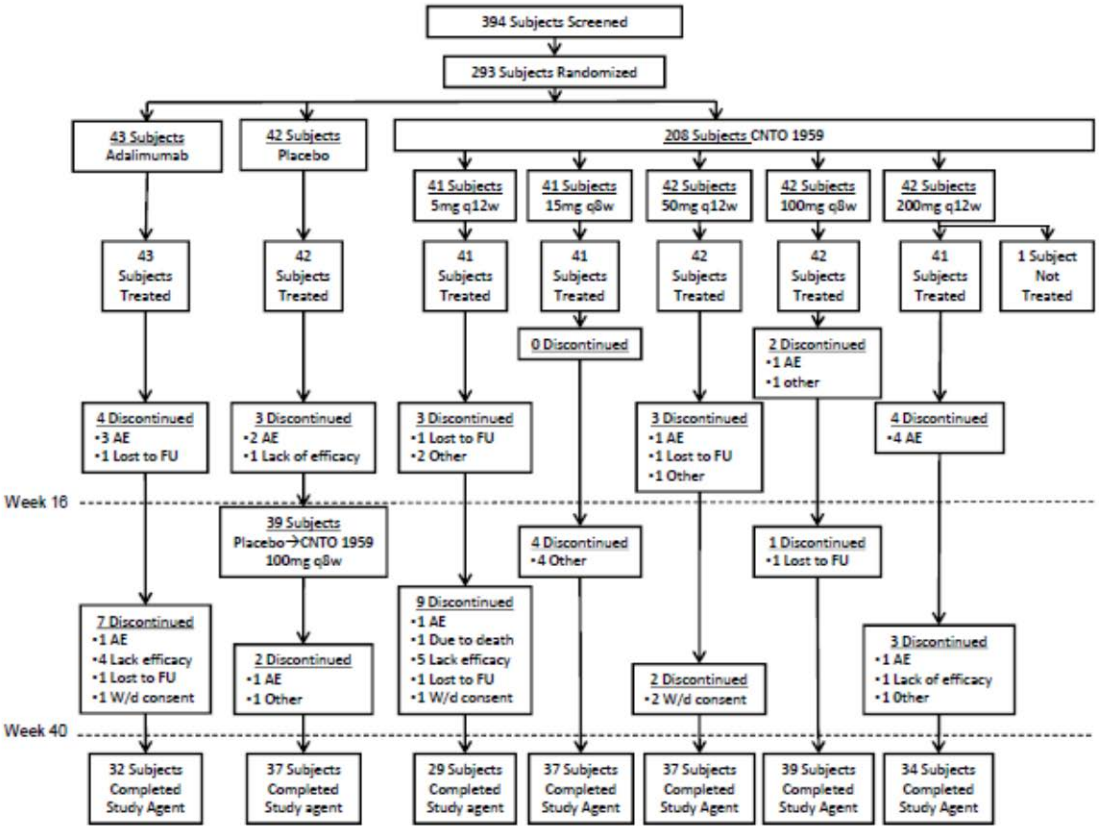
7.1.4. Disposition

A total of 394 subjects were screened, 293 subjects were randomized, and 292 subjects were treated, as shown in Figure 2.

Figure 2. Subject Disposition Through Week 52 (Study 2001)



Key: AE=adverse event; Discontinued=discontinued study agent; FU=follow-up; W/d=withdrew. Extracted from TSITG01, TSITG02, TSIDS01A, TSIDS01B, LSIDS01.

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7.1.5. Demographic and Baseline Characteristics / Medical History

Clinical disease characteristics were similar between treatment groups. A higher percentage of subjects in the adalimumab treatment group had a family history of premature coronary artery disease (16.3%), hypertension (30.2%), and hyperlipidemia (25.6%), compared to other treatment groups.

TSIDEM01: Summary of Demographics at Baseline; Randomized Subjects

	CNTO 1959								
	Adalimumab	Placebo	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined	Total
Subjects randomized	43	42	41	41	42	42	42	208	293
Age (years)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	47.5 (14.91)	45.0 (11.97)	45.2 (13.92)	43.8 (13.50)	42.6 (12.14)	45.3 (13.72)	45.1 (10.96)	44.4 (12.81)	44.9 (13.02)
Median	50.0	46.5	43.0	45.0	44.5	41.5	46.0	44.0	45.0
Range	(21; 79)	(21; 65)	(18; 77)	(21; 74)	(22; 82)	(21; 72)	(23; 68)	(18; 82)	(18; 82)
IQ range	(34.0; 57.0)	(36.0; 55.0)	(38.0; 55.0)	(33.0; 51.0)	(34.0; 48.0)	(34.0; 57.0)	(38.0; 52.0)	(34.5; 53.0)	(35.0; 55.0)
Sex									
N	43	42	41	41	42	42	42	208	293
Male	30 (69.8%)	28 (66.7%)	28 (68.3%)	28 (68.3%)	30 (71.4%)	32 (76.2%)	31 (73.8%)	149 (71.6%)	207 (70.6%)
Female	13 (30.2%)	14 (33.3%)	13 (31.7%)	13 (31.7%)	12 (28.6%)	10 (23.8%)	11 (26.2%)	59 (28.4%)	86 (29.4%)
Race									
N	43	42	41	41	42	42	42	208	293
White	39 (90.7%)	39 (92.9%)	35 (85.4%)	40 (97.6%)	37 (88.1%)	38 (90.5%)	39 (92.9%)	189 (90.9%)	267 (91.1%)
Black or African American	1 (2.3%)	1 (2.4%)	2 (4.9%)	0	0	0	1 (2.4%)	3 (1.4%)	5 (1.7%)
Asian	3 (7.0%)	2 (4.8%)	3 (7.3%)	1 (2.4%)	5 (11.9%)	2 (4.8%)	1 (2.4%)	12 (5.8%)	17 (5.8%)
American Indian or Alaskan Native	0	0	0	0	0	1 (2.4%)	0	1 (0.5%)	1 (0.3%)
Native Hawaiian or other Pacific Islander	0	0	1 (2.4%)	0	0	0	1 (2.4%)	2 (1.0%)	2 (0.7%)
Other	0	0	0	0	0	1 (2.4%)	0	1 (0.5%)	1 (0.3%)
Unknown	0	0	0	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0	0	0	0
Ethnicity (Hispanic/Latino)									
N	43	42	41	41	42	42	42	208	293
Yes	5 (11.6%)	3 (7.1%)	3 (7.3%)	5 (12.2%)	4 (9.5%)	3 (7.1%)	4 (9.5%)	19 (9.1%)	27 (9.2%)
No	36 (83.7%)	39 (92.9%)	38 (92.7%)	35 (85.4%)	38 (90.5%)	39 (92.9%)	38 (90.5%)	188 (90.4%)	263 (89.8%)
Unknown	2 (4.7%)	0	0	1 (2.4%)	0	0	0	1 (0.5%)	3 (1.0%)
Not Reported	0	0	0	0	0	0	0	0	0
Weight (kg)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	91.6 (19.88)	93.6 (22.62)	93.8 (22.15)	87.3 (20.09)	88.7 (22.02)	91.2 (22.01)	92.7 (25.48)	90.7 (22.34)	91.3 (21.99)
Median	88.6	90.2	89.0	89.5	89.6	91.3	90.2	89.4	89.5
Range	(51; 148)	(56; 162)	(45; 159)	(51; 129)	(49; 175)	(56; 148)	(52; 172)	(45; 175)	(45; 175)
IQ range	(78.0; 105.0)	(80.3; 103.4)	(82.4; 105.0)	(70.0; 102.0)	(73.0; 100.0)	(72.4; 104.0)	(76.7; 103.0)	(76.4; 103.0)	(76.5; 103.3)
≤ 90 kg	23 (53.5%)	21 (50.0%)	21 (51.2%)	22 (53.7%)	21 (50.0%)	21 (50.0%)	21 (50.0%)	106 (51.0%)	150 (51.2%)
> 90 kg	20 (46.5%)	21 (50.0%)	20 (48.8%)	19 (46.3%)	21 (50.0%)	21 (50.0%)	21 (50.0%)	102 (49.0%)	143 (48.8%)
Height (cm)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	173.1 (8.80)	173.1 (8.52)	173.4 (8.04)	171.3 (9.29)	172.2 (9.99)	172.2 (9.87)	172.2 (9.94)	172.3 (9.39)	172.5 (9.17)
Median	172.0	174.0	173.0	172.0	172.0	173.0	172.0	172.0	173.0
Range	(155; 188)	(158; 192)	(158; 189)	(152; 190)	(154; 197)	(147; 197)	(147; 188)	(147; 197)	(147; 197)
IQ range	(167.0; 181.0)	(167.0; 180.0)	(167.0; 180.0)	(165.0; 178.0)	(165.0; 178.0)	(167.0; 180.0)	(168.0; 180.0)	(165.5; 180.0)	(167.0; 180.0)
BMI (kg/m^2)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	30.5 (5.84)	31.2 (6.98)	31.1 (6.46)	29.6 (6.07)	29.8 (6.01)	30.7 (6.79)	31.1 (7.50)	30.4 (6.56)	30.6 (6.50)
Median	29.9	28.8	30.3	29.2	29.2	30.3	28.9	29.8	29.8
Range	(19; 43)	(19; 47)	(17; 47)	(20; 42)	(19; 45)	(21; 56)	(20; 58)	(17; 58)	(17; 58)
IQ range	(25.3; 34.9)	(26.6; 35.7)	(27.4; 34.6)	(24.8; 34.0)	(25.7; 34.1)	(24.9; 34.9)	(25.7; 34.3)	(25.8; 34.3)	(25.8; 34.5)

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TSIDEM02: Summary of Clinical Disease Characteristics at Baseline; Randomized Subjects

	CNTO 1959								
	Adalimumab	Placebo	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined	Total
Subjects randomized	43	42	41	41	42	42	42	208	293
Psoriasis disease duration (yrs)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	19.3 (12.79)	18.0 (13.30)	19.5 (13.44)	17.3 (11.69)	18.0 (11.30)	18.3 (12.29)	19.4 (12.50)	18.5 (12.17)	18.6 (12.39)
Median	18.3	15.4	17.3	14.5	16.5	16.5	16.6	16.4	16.4
Range	(2; 57)	(1; 43)	(1; 47)	(1; 40)	(1; 46)	(1; 48)	(1; 49)	(1; 49)	(1; 57)
IQ range	(9.3; 25.5)	(5.4; 31.2)	(6.8; 30.0)	(8.6; 25.2)	(9.3; 25.1)	(7.2; 24.5)	(9.3; 30.0)	(8.3; 26.1)	(8.6; 26.3)
Age at diagnosis (yrs)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	28.3 (13.52)	26.9 (13.79)	25.7 (14.68)	26.5 (15.06)	24.5 (13.91)	27.1 (14.84)	25.9 (14.74)	26.0 (14.53)	26.4 (14.26)
Median	26.0	24.5	22.0	25.0	21.0	23.0	22.5	22.5	23.0
Range	(7; 63)	(3; 56)	(3; 57)	(5; 63)	(1; 70)	(8; 69)	(2; 61)	(1; 70)	(1; 70)
IQ range	(17.0; 35.0)	(16.0; 36.0)	(13.0; 35.0)	(15.0; 38.0)	(17.0; 31.0)	(17.0; 36.0)	(17.0; 33.0)	(16.0; 35.0)	(16.0; 35.0)
BSA (%)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	26.8 (16.80)	27.5 (19.26)	24.9 (15.07)	26.2 (17.81)	25.6 (12.81)	24.5 (15.55)	21.9 (10.56)	24.6 (14.48)	25.3 (15.58)
Median	20.0	22.0	21.0	20.0	21.5	20.5	17.5	20.0	20.0
Range	(10; 80)	(10; 89)	(10; 80)	(10; 80)	(11; 53)	(11; 80)	(10; 50)	(10; 80)	(10; 89)
IQ range	(14.0; 40.0)	(13.0; 30.0)	(14.0; 30.0)	(14.0; 35.0)	(14.0; 35.0)	(13.0; 27.0)	(14.0; 29.0)	(14.0; 30.5)	(14.0; 31.0)
BSA									
N	43	42	41	41	42	42	42	208	293
≥ 20%	23 (53.5%)	24 (57.1%)	24 (58.5%)	22 (53.7%)	23 (54.8%)	24 (57.1%)	18 (42.9%)	111 (53.4%)	158 (53.9%)
< 20%	20 (46.5%)	18 (42.9%)	17 (41.5%)	19 (46.3%)	19 (45.2%)	18 (42.9%)	24 (57.1%)	97 (46.6%)	135 (46.1%)
PASI score (0-72)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	20.22 (7.576)	21.76 (9.978)	20.94 (7.130)	21.48 (10.019)	22.32 (8.994)	20.36 (7.709)	19.44 (5.886)	20.90 (8.053)	20.93 (8.269)
Median	17.90	17.25	20.20	16.80	19.35	18.25	18.10	18.45	18.20
Range	(12.2; 40.8)	(11.9; 55.2)	(12.0; 40.3)	(12.0; 49.6)	(12.2; 49.1)	(12.0; 51.1)	(12.1; 36.0)	(12.0; 51.1)	(11.9; 55.2)
IQ range	(14.00; 23.40)	(14.90; 24.60)	(15.70; 25.40)	(14.80; 25.80)	(16.00; 25.10)	(15.20; 23.60)	(14.40; 23.00)	(15.15; 24.20)	(15.00; 24.30)
PASI score									
N	43	42	41	41	42	42	42	208	293
≥ 20	19 (44.2%)	18 (42.9%)	21 (51.2%)	16 (39.0%)	19 (45.2%)	17 (40.5%)	16 (38.1%)	89 (42.8%)	126 (43.0%)
< 20	24 (55.8%)	24 (57.1%)	20 (48.8%)	25 (61.0%)	23 (54.8%)	25 (59.5%)	26 (61.9%)	119 (57.2%)	167 (57.0%)
PGA score									
N	43	42	41	41	42	42	42	208	293
Cleared (0)	0	0	0	0	0	0	0	0	0
Minimal (1)	0	0	0	0	0	0	0	0	0
Mild (2)	1 (2.3%)	0	0	0	0	0	0	0	1 (0.3%)
	Adalimumab	Placebo	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined	Total
Moderate (3)	24 (55.8%)	22 (52.4%)	19 (46.3%)	25 (61.0%)	23 (54.8%)	28 (66.7%)	21 (50.0%)	116 (55.8%)	162 (55.3%)
Marked (4)	14 (32.6%)	19 (45.2%)	18 (43.9%)	13 (31.7%)	19 (45.2%)	12 (28.6%)	19 (45.2%)	81 (38.9%)	114 (38.9%)
Severe (5)	4 (9.3%)	1 (2.4%)	4 (9.8%)	3 (7.3%)	0	2 (4.8%)	2 (4.8%)	11 (5.3%)	16 (5.5%)
PGA score									
N	43	42	41	41	42	42	42	208	293
Marked or severe (≥ 4)	18 (41.9%)	20 (47.6%)	22 (53.7%)	16 (39.0%)	19 (45.2%)	14 (33.3%)	21 (50.0%)	92 (44.2%)	130 (44.4%)
DLQI (0-30)									
N	43	42	41	41	42	42	42	208	293
Mean (SD)	14.60 (7.172)	14.62 (5.906)	12.37 (6.316)	15.34 (7.289)	15.36 (7.544)	13.19 (6.696)	13.64 (7.355)	13.98 (7.089)	14.16 (6.929)
Median	13.00	14.00	13.00	15.00	16.00	14.00	14.00	14.00	14.00
Range	(3.0; 28.0)	(5.0; 27.0)	(1.0; 29.0)	(3.0; 30.0)	(3.0; 30.0)	(2.0; 27.0)	(1.0; 27.0)	(1.0; 30.0)	(1.0; 30.0)
IQ range	(9.00; 21.00)	(9.00; 20.00)	(7.00; 17.00)	(9.00; 20.00)	(9.00; 21.00)	(8.00; 18.00)	(7.00; 17.00)	(8.00; 19.00)	(9.00; 19.00)
Subjects were diagnosed with Psoriatic arthritis at baseline	11 (25.6%)	12 (28.6%)	10 (24.4%)	8 (19.5%)	11 (26.2%)	8 (19.0%)	15 (35.7%)	52 (25.0%)	75 (25.6%)
Subjects were diagnosed with Scalp Psoriasis at baseline	39 (90.7%)	41 (97.6%)	38 (92.7%)	36 (87.8%)	42 (100.0%)	40 (95.2%)	36 (85.7%)	192 (92.3%)	272 (92.8%)

[TSIDEM02.rtf] [CNTO1959\PSO2001\DBR_WEEK_052\RE_WEEK_052_CSR\TSIDEM02.sas] 09OCT2013, 14:31

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Reference ID: 4084700

TSIDEM03: Summary of Medical History and Current Diagnoses; Randomized Subjects

			CNTO 1959						
	Adalimumab	Placebo	5 mg q12w	15 mg q8w	50 mg q12w	100 mg q8w	200 mg q12w	Combined	Total
Subjects randomized	43	42	41	41	42	42	42	208	293
Coronary artery disease	3 (7.0%)	1 (2.4%)	0	0	0	0	1 (2.4%)	1 (0.5%)	5 (1.7%)
Myocardial infarction	3 (7.0%)	0	0	0	0	0	1 (2.4%)	1 (0.5%)	4 (1.4%)
Angina pectoris	1 (2.3%)	1 (2.4%)	0	0	0	0	0	0	2 (0.7%)
Coronary artery bypass graft	1 (2.3%)	0	0	0	0	0	0	0	1 (0.3%)
Percutaneous coronary intervention	1 (2.3%)	1 (2.4%)	0	0	0	0	0	0	2 (0.7%)
Peripheral vascular disease	0	0	1 (2.4%)	0	0	0	2 (4.8%)	3 (1.4%)	3 (1.0%)
Transient ischemic attack	2 (4.7%)	0	0	0	1 (2.4%)	0	0	1 (0.5%)	3 (1.0%)
Stroke	0	0	0	0	0	0	1 (2.4%)	1 (0.5%)	1 (0.3%)
Family history of early coronary artery disease (<55 years of age)	7 (16.3%)	3 (7.1%)	2 (4.9%)	3 (7.3%)	2 (4.8%)	2 (4.8%)	1 (2.4%)	10 (4.8%)	20 (6.8%)
Diabetes mellitus	3 (7.0%)	4 (9.5%)	6 (14.6%)	4 (9.8%)	3 (7.1%)	3 (7.1%)	4 (9.5%)	20 (9.6%)	27 (9.2%)
Hypertension	13 (30.2%)	13 (31.0%)	12 (29.3%)	7 (17.1%)	12 (28.6%)	9 (21.4%)	13 (31.0%)	53 (25.5%)	79 (27.0%)
Hyperlipidemia	11 (25.6%)	8 (19.0%)	11 (26.8%)	6 (14.6%)	6 (14.3%)	7 (16.7%)	7 (16.7%)	37 (17.8%)	56 (19.1%)
Skin squamous cell cancer carcinoma(SCC)	1 (2.3%)	0	1 (2.4%)	0	0	0	1 (2.4%)	2 (1.0%)	3 (1.0%)
Skin basal cell cancer carcinoma(BCC)	1 (2.3%)	0	1 (2.4%)	0	1 (2.4%)	1 (2.4%)	1 (2.4%)	4 (1.9%)	5 (1.7%)
Family history of cancer in a 1st degree relative (excluding skin squamous cell cancer carcinoma and skin basal cell cancer carcinoma)	11 (25.6%)	6 (14.3%)	9 (22.0%)	5 (12.2%)	6 (14.3%)	4 (9.5%)	11 (26.2%)	35 (16.8%)	52 (17.7%)
Asthma	4 (9.3%)	1 (2.4%)	4 (9.8%)	1 (2.4%)	3 (7.1%)	4 (9.5%)	1 (2.4%)	13 (6.3%)	18 (6.1%)
Depression	1 (2.3%)	7 (16.7%)	4 (9.8%)	3 (7.3%)	3 (7.1%)	2 (4.8%)	4 (9.5%)	16 (7.7%)	24 (8.2%)
Chronic liver disease	0	0	0	0	0	0	1 (2.4%)	1 (0.5%)	1 (0.3%)
Hospitalized within past 1 year (excluding pregnancy)	3 (7.0%)	5 (11.9%)	6 (14.6%)	3 (7.3%)	4 (9.5%)	3 (7.1%)	5 (11.9%)	21 (10.1%)	29 (9.9%)
Hospitalized within the past year for an infection	0	0	1 (2.4%)	0	1 (2.4%)	0	0	2 (1.0%)	2 (0.7%)
Does this patient drink alcohol	24 (55.8%)	24 (57.1%)	24 (58.5%)	23 (56.1%)	24 (57.1%)	26 (61.9%)	22 (52.4%)	119 (57.2%)	167 (57.0%)
Smoking (past or current)	25 (58.1%)	24 (57.1%)	23 (56.1%)	24 (58.5%)	24 (57.1%)	24 (57.1%)	17 (40.5%)	112 (53.8%)	161 (54.9%)
Still smoking	13 (30.2%)	15 (35.7%)	16 (39.0%)	13 (31.7%)	16 (38.1%)	15 (35.7%)	9 (21.4%)	69 (33.2%)	97 (33.1%)

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7.1.6. CEC-Adjudicated Cardiovascular Events

CEC-adjudicated events are summarized in Tables 3 and 4.

Table 3. Study 2001: CEC-Adjudicated Cardiovascular Events (Through Week 52)

	Adalimumab (US)*	Adalimumab (EU)**	Placebo	Guselkumab 5 mg q 12w	Guselkumab 15 mg q 8w	Guselkumab 50 mg q 12w	Guselkumab 100 mg q 8w	Guselkumab 200 mg q 12w	Combined	All Guselkumab
# of subjects treated	21	22	39	41	41	42	42	41	207	246
Total subject-years of follow-up	17	21	27	35	39	40	40	38	192	219
MACE										
# of Events (%)	0	0	0	1 (2.44)	0	0	2 (4.76)	0	3 (1.45)	3 (1.22)
100 Subject-years	0	0	0	2.86	0	0	5.00	0	1.56	1.37
CV death										
# of Events (%)	0	0	0	1 (2.44)	0	0	0	0	1 (0.48)	1 (0.41)
100 Subject-years	0	0	0	2.86	0	0	0	0	0.52	0.46
Nonfatal MI										
# of Events (%)							1 (2.38)		1 (0.48)	1 (0.41)
100 Subject-years							2.50		0.52	0.46
Nonfatal Stroke										
# of Events (%)							1 (2.38)†		1 (0.48)†	1 (0.41)†
100 Subject-years							2.50		0.52	0.46
All-Cause Mortality										
# of Events (%)				1 (2.44)					1 (0.48)	1 (0.41)
100 Subject-years				2.86					0.52	0.46
Other CV Events										
# of Events (%)	2 (9.52)	0	0	0	0	0	0	0	0	0
100 Subject-years	11.8	0	0	0	0	0	0	0	0	0
Arrhythmia Requiring Intervention										
# of Events (%)	2 (9.52)	0	0	0	0	0	0	0	0	0
100 Subject-years	11.8	0	0	0	0	0	0	0	0	0

EU: European Union-approved adalimumab; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction; w: weeks.
The "Combined Guselkumab" group includes guselkumab treatment groups, and the "All Guselkumab" group includes all guselkumab treatment groups as well as placebo subjects crossing over to guselkumab treatment (guselkumab 100 mg subcutaneous [SC] administration at Week 16 and q 8 weeks thereafter through Week 40).
*The US-licensed adalimumab group includes US subjects only (does not include Canadian subjects).
**The European Union approved adalimumab group includes subjects outside of the US who received EU-approved adalimumab.
†This subject was identified by Dr. Hicks. The Clinical Events Committee (CEC) was queried. Although the CEC had initially adjudicated this event as "Not a Stroke," upon the query, the CEC reviewed the case and according to the sponsor, "noted that an administrative error resulted in the wrong source documentation being associated with subject 00193." This event was re-adjudicated by the CEC to be an "ischemic stroke."
Analysis by Ququan Liu, MD, MS (Division of Biometrics 1)

Table 4. Study 2001: CEC-Adjudicated Treatment Emergent Serious Cardiovascular Events

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category[a]	CEC Detailed Event Type[a]	Serious (Y/N)[b]	Reviewer Category and Comments
1	Guselkumab 5 mg	CNTO1959PSO2001-0103-00206 55 yo white male (Canada)	Guselkumab	114	(b) (6)	208	Myocardial Infarction (MYOCARDIAL INFARCTION)	CV death	Other type of MI	Y	CV death due to AMI (no major CV risk factors)
2	Guselkumab 100 mg	CNTO1959PSO2001-0108-00393 69 yo white female (Canada)	Guselkumab	235	(b) (6)	248	Myocardial infarction (MYOCARDIAL INFARCTION)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (no major CV risk factors)
3	Guselkumab 100 mg	CNTO1050PSO2001-0022-00193 70 yo white female (USA)	Guselkumab	279	(b) (6)	292	Cerebral vascular accident	Initially adjudicated as not an event. Following FDA query, the CEC re-adjudicated this event as an Ischemic Stroke	Ischemic Stroke	Y	Ischemic Stroke (history of HTN and HLP)
4	Adalimumab	CNTO1959PSO2001-0011-00159 79 yo white male (USA)	Adalimumab	50	(b) (6)	65	Atrial flutter (ATRIAL FLUTTER)	Arrhythmia Requiring Intervention	Other Arrhythmia [Atrial Flutter]	Y	Arrhythmia Requiring Intervention (Atrial Flutter) (history of basal cell and squamous cell carcinoma of the skin)
5				50	(b) (6)	89	Atrial flutter (ATRIAL FLUTTER)	Arrhythmia Requiring Intervention	Other Arrhythmia [Atrial Flutter]	Y	Arrhythmia Requiring Intervention (Atrial Flutter)

AMI: acute myocardial infarction; CEC: Clinical Events Committee; CV: cardiovascular; HLP: hyperlipidemia; HTN: hypertension; MI: myocardial infarction; N: no; Y: yes; yo: year old
[a]Determined by Clinical Events Committee (CEC)
[b]Adjudicated Cardiovascular (CV) Events include serious events only
Adapted from Sponsor. Response to Information Request dated March 24, 2017.

7.2. Study 3001

Study 3001 was a phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study in patients with moderate to severe plaque-type psoriasis who were candidates for either systemic therapy or phototherapy and may have received some systemic therapies or phototherapy for psoriasis previously.

7.2.1. Key Inclusion Criteria

Inclusion criteria were similar to Study 2001.

7.2.2. Key Exclusion Criteria

Exclusion criteria were similar to Study 2001.

7.2.3. Treatment Groups and Study Design

The study consisted of

- a blinded treatment period (Week 0 through Week 48); and
- an open-label treatment period (Week 48 through Week 160)

At Week 0, eligible subjects were randomized in a 2:1:2 fashion to 1 of 3 treatment groups as follows:

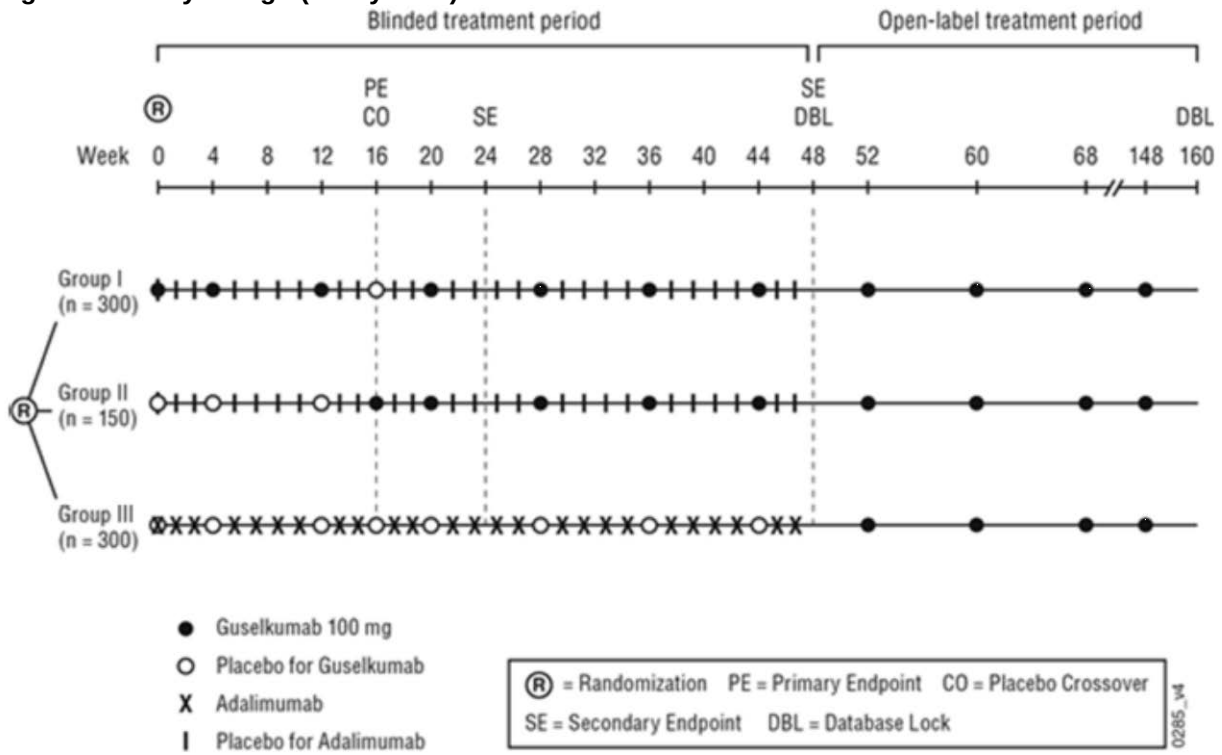
- Group I (guselkumab 100 mg at Weeks 0, 4, and 12, and every 8 weeks (q8w) thereafter through Week 44
- Group II (placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20 and q8w thereafter through Week 44
- Group III (adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks (q2w) thereafter through Week 47)

During the open-label treatment period (Week 48 through Week 160), all subjects were to receive guselkumab. Subjects in Groups I and II continued to receive guselkumab 100 mg at Week 52 and q8w thereafter through Week 148. Subjects in Group III entered a washout period after their final dose of adalimumab at Week 47 and began guselkumab 100 mg at Week 52 and q8w thereafter through Week 148. Database locks were planned for Weeks 48 and 160.

Figure 3 summarizes the study design.

Reference ID: 4084700

Figure 3. Study Design (Study 3001)



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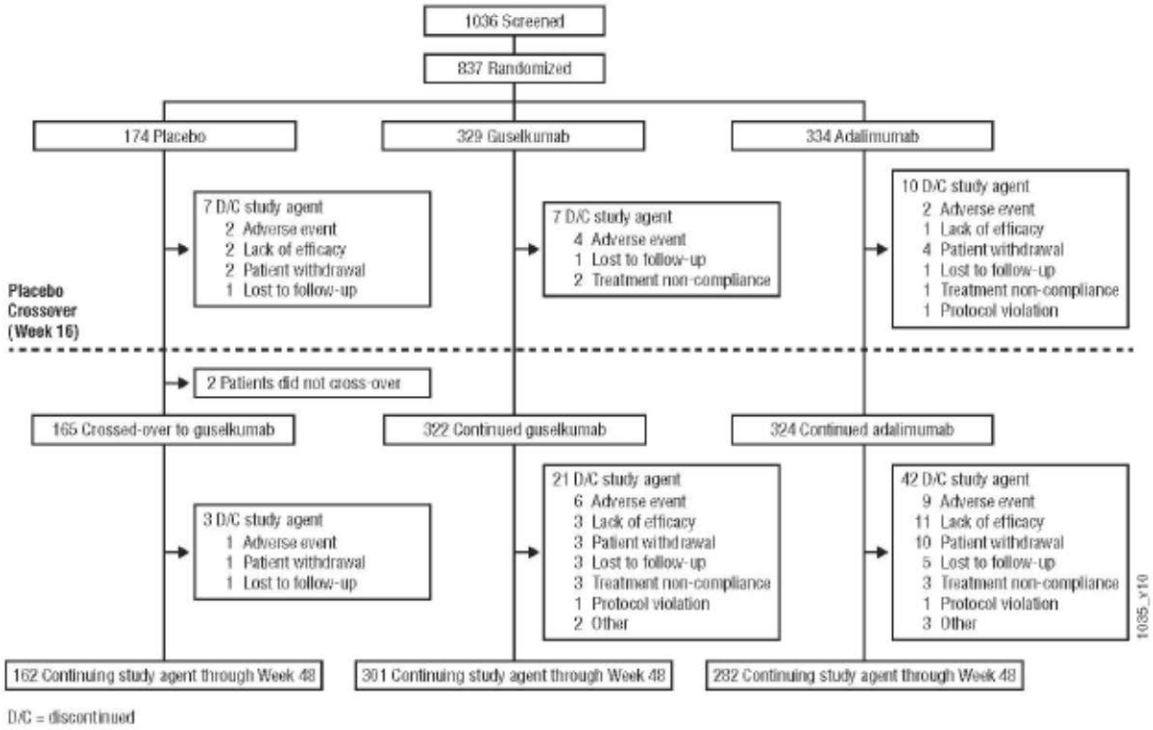
7.2.4. Disposition

A total of 1,036 subjects were screened, 837 subjects were randomized, and 836 subjects were treated, including 174 placebo, 329 guselkumab, and 333 adalimumab subjects, as shown in Figure 4.

Figure 4. Subject Disposition (Study 3001)



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.

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7.2.5. Demographic and Baseline Characteristics / Medical History

Clinical disease characteristics were similar between treatment groups. A higher percentage of subjects in the placebo treatment group had a history of diabetes, hyperlipidemia, and a family history of premature coronary artery disease, compared to other treatment groups.

TSIDEM01A: Summary of Demographics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0	174	329	334	837
Age (years)				
N	174	329	334	837
Mean (SD)	44.9 (12.90)	43.9 (12.74)	42.9 (12.58)	43.7 (12.72)
Median	45.0	43.0	43.0	44.0
Range	(19; 77)	(19; 76)	(18; 87)	(18; 87)
IQ range	(36.0; 54.0)	(33.0; 54.0)	(33.0; 52.0)	(33.0; 53.0)
Sex				
N	174	329	334	837
Male	119 (68.4%)	240 (72.9%)	249 (74.6%)	608 (72.6%)
Female	55 (31.6%)	89 (27.1%)	85 (25.4%)	229 (27.4%)
Race				
N	174	329	334	837
White	145 (83.3%)	262 (79.6%)	277 (82.9%)	684 (81.7%)
Black or African American	3 (1.7%)	6 (1.8%)	8 (2.4%)	17 (2.0%)
Asian	23 (13.2%)	51 (15.5%)	47 (14.1%)	121 (14.5%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	1 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.4%)
Other	2 (1.1%)	7 (2.1%)	1 (0.3%)	10 (1.2%)
Multiple	0	2 (0.6%)	0	2 (0.2%)
Unknown	0	0	0	0
Not Reported	0	0	0	0
Ethnicity (Hispanic/Latino)				
N	174	329	334	837
Yes	19 (10.9%)	16 (4.9%)	30 (9.0%)	65 (7.8%)
No	153 (87.9%)	309 (93.9%)	297 (88.9%)	759 (90.7%)
Unknown	0	2 (0.6%)	3 (0.9%)	5 (0.6%)
Not Reported	2 (1.1%)	2 (0.6%)	4 (1.2%)	8 (1.0%)
Weight (kg)				
N	174	329	333	836
Mean (SD)	88.0 (24.44)	89.5 (20.11)	90.5 (21.84)	89.6 (21.75)
Median	83.0	87.1	87.1	86.5
Range	(48; 169)	(48; 161)	(41; 174)	(41; 174)
IQ range	(70.9; 97.0)	(76.6; 100.0)	(75.0; 102.8)	(75.0; 100.0)
≤ 90 kg	111 (63.8%)	189 (57.4%)	191 (57.4%)	491 (58.7%)
> 90 kg	63 (36.2%)	140 (42.6%)	142 (42.6%)	345 (41.3%)
Height (cm)				
N	174	329	333	836
Mean (SD)	173.9 (9.58)	173.5 (9.41)	173.9 (9.73)	173.7 (9.57)
Median	172.7	174.0	175.0	174.0
Range	(142; 198)	(146; 196)	(142; 208)	(142; 208)
IQ range	(168.0; 180.0)	(168.0; 180.0)	(167.5; 180.0)	(167.7; 180.0)
BMI (kg/m^2)				
N	174	329	333	836
Mean (SD)	28.9 (6.89)	29.7 (6.22)	29.8 (6.48)	29.6 (6.47)

Reference ID: 4084700

TSIDEM01A: Summary of Demographics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Median	27.3	28.7	28.7	28.4
Range	(18; 52)	(19; 54)	(16; 65)	(16; 65)
IQ range	(24.1; 33.1)	(25.5; 32.9)	(25.2; 33.5)	(25.2; 33.2)

[TSIDEM01A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM01A.SAS] 12AUG2016, 13:04

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TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0	174	329	334	837
Psoriasis disease duration (yrs)				
N	174	329	334	837
Mean (SD)	17.6 (12.44)	17.9 (12.27)	17.0 (11.27)	17.5 (11.91)
Median	14.5	15.0	15.0	15.0
Range	(1; 64)	(1; 58)	(1; 59)	(1; 64)
IQ range	(8.3; 24.0)	(8.9; 25.0)	(8.6; 24.0)	(8.5; 24.1)
Age at diagnosis (yrs)				
N	174	329	334	837
Mean (SD)	27.4 (13.69)	26.0 (13.45)	26.0 (12.73)	26.3 (13.21)
Median	27.0	23.0	24.0	24.0
Range	(0; 58)	(1; 68)	(0; 77)	(0; 77)
IQ range	(17.0; 36.0)	(16.0; 35.0)	(18.0; 34.0)	(17.0; 35.0)
Subjects with psoriatic arthritis at baseline	30 (17.2%)	64 (19.5%)	62 (18.6%)	156 (18.6%)
Subjects with scalp psoriasis at baseline	150 (86.2%)	291 (88.4%)	295 (88.3%)	736 (87.9%)
Subjects with nail psoriasis at baseline	99 (56.9%)	198 (60.2%)	194 (58.1%)	491 (58.7%)
Subjects with hand and/or foot psoriasis at baseline	44 (25.3%)	100 (30.4%)	101 (30.2%)	245 (29.3%)
BSA(%)				
N	174	329	334	837
Mean (SD)	25.8 (15.93)	28.3 (17.10)	28.6 (16.66)	27.9 (16.70)
Median	20.0	22.0	23.0	22.0
Range	(10; 85)	(10; 90)	(10; 85)	(10; 90)
IQ range	(14.0; 31.0)	(15.0; 35.0)	(15.0; 38.0)	(15.0; 36.0)
BSA				
N	174	329	334	837
≥ 20%	88 (50.6%)	198 (60.2%)	202 (60.5%)	488 (58.3%)
< 20%	86 (49.4%)	131 (39.8%)	132 (39.5%)	349 (41.7%)
PASI score (0-72)				
N	174	329	334	837
Mean (SD)	20.39 (8.737)	22.10 (9.491)	22.36 (8.974)	21.85 (9.154)
Median	17.40	18.60	20.00	19.00
Range	(12.0; 61.0)	(12.0; 68.4)	(7.0; 58.0)	(7.0; 68.4)
IQ range	(14.40; 23.10)	(15.60; 25.50)	(16.00; 26.10)	(15.40; 25.40)
PASI score				
N	174	329	334	837
≥ 20	63 (36.2%)	143 (43.5%)	167 (50.0%)	373 (44.6%)
< 20	111 (63.8%)	186 (56.5%)	167 (50.0%)	464 (55.4%)
IGA score				
N	174	329	334	837
Cleared (0)	0	0	0	0
Minimal (1)	0	0	0	0
Mild (2)	0	0	3 (0.9%)	3 (0.4%)
Moderate (3)	131 (75.3%)	252 (76.6%)	241 (72.2%)	624 (74.6%)
Severe (4)	43 (24.7%)	77 (23.4%)	90 (26.9%)	210 (25.1%)

Reference ID: 4084700

TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
ss-IGA score				
N	150	291	295	736
Absence of disease (0)	0	0	0	0
Very mild (1)	5 (3.3%)	14 (4.8%)	9 (3.1%)	28 (3.8%)
Mild (2)	31 (20.7%)	49 (16.8%)	54 (18.3%)	134 (18.2%)
Moderate (3)	89 (59.3%)	171 (58.8%)	175 (59.3%)	435 (59.1%)
Severe (4)	25 (16.7%)	57 (19.6%)	57 (19.3%)	139 (18.9%)
f-PGA score				
N	99	198	194	491
Cleared (0)	0	0	0	0
Minimal (1)	11 (11.1%)	24 (12.1%)	21 (10.8%)	56 (11.4%)
Mild (2)	33 (33.3%)	62 (31.3%)	66 (34.0%)	161 (32.8%)
Moderate (3)	42 (42.4%)	83 (41.9%)	90 (46.4%)	215 (43.8%)
Severe (4)	13 (13.1%)	29 (14.6%)	17 (8.8%)	59 (12.0%)
NAPSI score (0-8)				
N	99	194	191	484
Mean (SD)	4.7 (1.94)	4.9 (2.03)	4.6 (2.03)	4.7 (2.01)
Median	4.0	5.0	4.0	4.0
Range	(1; 8)	(1; 8)	(1; 8)	(1; 8)
IQ range	(4.0; 6.0)	(4.0; 6.0)	(3.0; 6.0)	(4.0; 6.0)
hf-PGA score				
N	44	100	101	245
Cleared (0)	0	0	0	0
Almost Cleared (1)	1 (2.3%)	10 (10.0%)	6 (5.9%)	17 (6.9%)
Mild (2)	15 (34.1%)	34 (34.0%)	37 (36.6%)	86 (35.1%)
Moderate (3)	21 (47.7%)	42 (42.0%)	45 (44.6%)	108 (44.1%)
Severe (4)	7 (15.9%)	14 (14.0%)	13 (12.9%)	34 (13.9%)

[TSIDEM02A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM02A.SAS] 29MAY2016, 06:00

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TSIDEM04A: Summary of Medical History and Current Diagnoses; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects Randomized at Week 0	174	329	334	837
Coronary Artery Disease	5 (2.9%)	7 (2.1%)	8 (2.4%)	20 (2.4%)
Myocardial Infarction	4 (2.3%)	4 (1.2%)	3 (0.9%)	11 (1.3%)
Angina Pectoris	4 (2.3%)	2 (0.6%)	2 (0.6%)	8 (1.0%)
Coronary Artery Bypass Graft	0	0	1 (0.3%)	1 (0.1%)
Percutaneous Coronary Intervention	4 (2.3%)	1 (0.3%)	1 (0.3%)	6 (0.7%)
Peripheral Vascular Disease	3 (1.7%)	1 (0.3%)	5 (1.5%)	9 (1.1%)
Transient Ischemic Attack (TIA)	1 (0.6%)	0	1 (0.3%)	2 (0.2%)
Stroke	0	2 (0.6%)	2 (0.6%)	4 (0.5%)
Diabetes Mellitus	16 (9.2%)	22 (6.7%)	30 (9.0%)	68 (8.1%)
Hyperlipidemia	31 (17.8%)	48 (14.6%)	41 (12.3%)	120 (14.3%)
Hypertension	42 (24.1%)	80 (24.3%)	80 (24.0%)	202 (24.1%)
Use of Cigarettes				
Current or former smoker	81 (46.6%)	186 (56.5%)	166 (49.7%)	433 (51.7%)
Current smoker	48 (27.6%)	106 (32.2%)	100 (29.9%)	254 (30.3%)
Never used	93 (53.4%)	143 (43.5%)	168 (50.3%)	404 (48.3%)
Smoking pack years*				
N	81	185	165	431
Mean (SD)	16.31 (13.644)	16.77 (14.104)	16.65 (14.787)	16.64 (14.254)
Median	14.00	13.13	12.08	13.00
Range	(0.2; 66.0)	(0.0; 76.1)	(0.0; 82.0)	(0.0; 82.0)
IQ range	(5.27; 26.00)	(5.14; 24.00)	(5.23; 24.09)	(5.14; 24.09)
Family history of Early Coronary Artery Disease (< 55 years of age)	16 (9.2%)	21 (6.4%)	20 (6.0%)	57 (6.8%)
Asthma	11 (6.3%)	13 (4.0%)	21 (6.3%)	45 (5.4%)
Depression	14 (8.0%)	21 (6.4%)	27 (8.1%)	62 (7.4%)
Chronic Liver Disease (e.g., fatty liver disease, alcohol-induced, cirrhosis)	5 (2.9%)	13 (4.0%)	13 (3.9%)	31 (3.7%)
Hospitalized within the past year(excluding pregnancy)	8 (4.6%)	32 (9.7%)	25 (7.5%)	65 (7.8%)
Hospitalized within the past year for infection	1 (0.6%)	1 (0.3%)	0	2 (0.2%)
Skin Squamous Cell Carcinoma (SCC)	1 (0.6%)	0	0	1 (0.1%)

Reference ID: 4084700

TSIDEM04A: Summary of Medical History and Current Diagnoses; Subjects Randomized at Week 0 (Study CNTO1959PSO3001)				
	Placebo	Guselkumab	Adalimumab	Total
Skin Basal Cell Carcinoma (BCC)	4 (2.3%)	3 (0.9%)	1 (0.3%)	8 (1.0%)
Other malignancy	2 (1.1%)	7 (2.1%)	3 (0.9%)	12 (1.4%)
Family history Cancer in a 1st Degree Relative (excluding skin squamous cellcarcinomas and basal cell carcinomas)	28 (16.1%)	63 (19.1%)	52 (15.6%)	143 (17.1%)
Use of Alcohol				
Current or former used	115 (66.1%)	228 (69.3%)	237 (71.0%)	580 (69.3%)
Current alcohol user	106 (60.9%)	205 (62.3%)	207 (62.0%)	518 (61.9%)
Never used	59 (33.9%)	101 (30.7%)	97 (29.0%)	257 (30.7%)

* Smoking pack years = number of years of smoking x number of pack of cigarettes per day.

[TSIDEM04A.RTF] [CNTO1959\PSO3001\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM04A.SAS] 29MAY2016, 06:01

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7.2.6. CEC-Adjudicated Cardiovascular Events

Table 5 and Table 6 summarize the CEC-adjudicated CV events through Week 48.

Table 5. Study 3001: CEC-Adjudicated Cardiovascular Events (Through Week 48)

	Adalimumab (US)*	Adalimumab (EU)	Placebo	Placebo to Guselkumab 100 mg	Guselkumab 100 mg	All Guselkumab**
# of subjects treated	115	218	174	165	329	494
Total subject-years of follow-up	99	192	53	101	294	395
MACE						
# of Events (%)	0	1 (0.46)	0	0	1 (0.30)	1 (0.20)
100 Subject-years	0	0.52	0	0	0.34	0.25
CV death						
# of Events (%)	0	0	0	0	0	0
100 Subject-years	0	0	0	0	0	0
Nonfatal MI						
# of Events (%)	0	1 (0.46)	0	0	1 (0.30)	1 (0.20)
100 Subject-years	0	0.52	0	0	0.34	0.25
Nonfatal Stroke						
# of Events (%)	0	0	0	0	0	0
100 Subject-years	0	0	0	0	0	0
All-Cause Mortality						
# of Events (%)	1 (0.87)	0	0	0	0	0
100 Subject-years	1.0	0	0	0	0	0
Non CV death						
# of Events (%)	1 (0.87)	0	0	0	0	0
100 Subject-years	1.0	0	0	0	0	0
Other CV Events						
# of Events (%)	0	4 (1.83)	0	1 (0.61)	0	1 (0.20)
100 Subject-years	0	2.08	0	1.0	0	0.25
Venous Thrombo-Embolic Event						
# of Events (%)	0	1 (0.46)	0	0	0	0
100 Subject-years	0	0.52	0	0	0	0

Reference ID: 4084700

	Adalimumab (US)*	Adalimumab (EU)	Placebo	Placebo to Guselkumab 100 mg	Guselkumab 100 mg	All Guselkumab**
Coronary Re-Vascularization (PCI, CABG)						
# of Events (%)	0	1 (0.46)	0	0	0	0
100 Subject-years	0	0.52	0	0	0	0
Heart Failure						
# of Events (%)	0	2 (0.92)	0	0	0	0
100 Subject-years	0	1.04	0	0	0	0
Arrhythmia Requiring Intervention						
# of Events (%)	0	0	0	1 (0.61)	0	0
100 Subject-years	0	0	0	1.0	0	0

CABG: coronary artery bypass graft surgery; EU: European Union-approved adalimumab; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction; PCI: percutaneous coronary intervention

*The US-licensed adalimumab group includes US and Canadian subjects.

**The "All Guselkumab" group includes all guselkumab treatment groups as well as placebo subjects crossing over to guselkumab treatment.

Analysis by Ruquan Liu, MD, MS (Division of Biometrics 1)

Table 6. Study 3001: CEC Adjudicated Treatment Emergent Cardiovascular Events (Through Week 48)

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category[a]	CEC Detailed Event Type[a]	Serious (Y/N)[b]	Reviewer Category and Comments
1	Placebo to Guselkumab 100 mg	CNTO1959PSO3001-DE00486-10553 54 yo white male (DEU)	Guselkumab	141	(b) (6)	163	Sinus node dysfunction (IMPLANTATION OF PACEMAKER/ SICK-SINUS SYNDROME)	Arrhythmia Requiring Intervention	Other Arrhythmia (Sinus node dysfunction)	Y	Arrhythmia Requiring Intervention (history of HLP and PVD)
2	Guselkumab 100 mg	CNTO1959PSO39001-CA00247-10282 63 yo white female (Canada)	Guselkumab	85	(b) (6)	85	Myocardial infarction (MYOCARDIAL INFARCTION)	Nonfatal myocardial infarction	Type 1: Spontaneous	Y	Nonfatal MI (Type 1) (history of HTN, HLP, smoking, obesity)
3	Adalimumab	CNTO1959PSO3001-AU00213-10011 34 yo Asian male (Australia)	Adalimumab	119	(b) (6)	126	Myocardial ischaemia (ISCHAEMIC HEART DISEASE)	Coronary revascularization (PCI, CABG)	PCI	Y	Coronary revascularization (PCI) (history of DM, HTN, HLP, obesity)
4		CNTO1959PSO3001-PL00235-10707 60 yo white male (Poland)	Adalimumab	288	(b) (6)	295	Venous thrombosis limb (PHLEBOTHROMBOSIS OF LOWER RIGHT LIMB)	VTE	Other Peripheral Venous Thrombosis [below knee DVT]	N	VTE (DVT) (history of DM, HTN, PVD, depression)
5		CNTO1959PSO3001-TW00035-10477 38 yo Asian male (Taiwan)	Adalimumab	61	(b) (6)	67	Cardiac Failure (HEART FAILURE)	HF	HF Hospitalization	Y	HF Hospitalization (history of depression)
6			Adalimumab	61	(b) (6)	127	Congestive cardiomyopathy (DILATED CARDIOMYOPATHY)	HF	HF Hospitalization	N	HF Hospitalization

Reference ID: 4084700

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category[a]	CEC Detailed Event Type[a]	Serious (Y/N)[b]	Reviewer Category and Comments
7		CNTO1959PSO3001-TW00035-10843 39 yo Asian male (Taiwan)	Adalimumab	21	(b) (6)	33	Acute myocardial infarction (Non-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (Type 1) (history of CAD, HTN, HLP)

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CEC: Clinical Events Committee; CV: cardiovascular; DVT: deep venous thrombosis;HLP: hyperlipidemia; HF: heart failure; HTN: hypertension; MI: myocardial infarction; N: no; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; VTE: venous thromboembolic event; Y: yes; yo: year old
[a]Determined by Clinical Events Committee (CEC)
[b]Adjudicated Cardiovascular (CV) Events include serious and nonserious events
Adapted from Sponsor. Response to Information Request dated March 24, 2017.

7.3. Study 3002

Study 3002 was a phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study in patients with moderate to severe plaque-type psoriasis who were candidates for either systemic therapy or phototherapy and may have received some systemic therapies or phototherapy for psoriasis previously.

7.3.1. Key Inclusion criteria

Inclusion criteria were similar to Study 2001.

7.3.2. Key Exclusion criteria

Exclusion criteria were similar to Study 2001.

7.3.3. Treatment Groups and Study Design

The study consisted of 3 phases:

- Placebo- and active-comparator-controlled treatment (Week 0 to Week 24)
- Randomized withdrawal and retreatment (Week 28 through Week 72)
- Open-label guselkumab treatment (Week 76 through Week 160

At Week 0, eligible subjects were randomized in a 2:1:1 fashion to 1 of 3 treatment groups:

- Group I: Guselkumab 100 mg at Weeks 0, 4, 12, and 20
- Group II: Placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20
- Group III: Adalimumab (80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and q2w thereafter through Week 23)

At Week 28, the randomized withdrawal and retreatment period began and continued through Week 72. Therapy during this time period was based on their level of response at Week 28:

- Subjects in Group I, randomized to guselkumab were treated as follows:
    - Group Ia: PASI 90 nonresponders at Week 28 continued on guselkumab 100 mg q8w beginning at Week 28
    - PASI90 responders at Week 28 were rerandomized in a 1:1 ratio to:
        - Group Ib: Guselkumab 100 mg q8w beginning at Week 28

Reference ID: 4084700

    - Group Ic: Placebo beginning at Week 28. Upon loss of ≥ 50% of the improvement in PASI achieved at Week 28, subjects were retreated with guselkumab 100 mg followed by a 100 mg dose 4 weeks later, and then guselkumab 100 mg q8w thereafter

- Subjects in Group II, randomized to placebo, were treated as follows:

  - Group IIa: PASI 90 nonresponders at Week 28 continued on guselkumab 100 mg q8w beginning at Week 28.
  - Group IIb: PASI 90 responders at Week 28 received placebo beginning at Week 28. If subjects lost ≥ 50% of the improvement in PASI achieved at Week 28, subjects were retreated with guselkumab 100 mg followed by a 100 mg dose 4 weeks later, and then guselkumab 100 mg q8w thereafter.

- Subjects in Group III, randomized to adalimumab, were treated as follows:

  - Group IIIa: PASI 90 nonresponders at Week 28 initiated guselkumab 100 mg at Week 28, followed by a 100 mg dose 4 weeks later, and then 100 mg q8w thereafter.
  - Group IIIb: PASI 90 responders at Week 28 received placebo beginning at Week 28. Upon loss of ≥ 50% of the improvement in PASI achieved at Week 28, subjects initiated guselkumab 100 mg followed by a 100 mg dose 4 weeks later, and then guselkumab 100 mg q 8w thereafter.

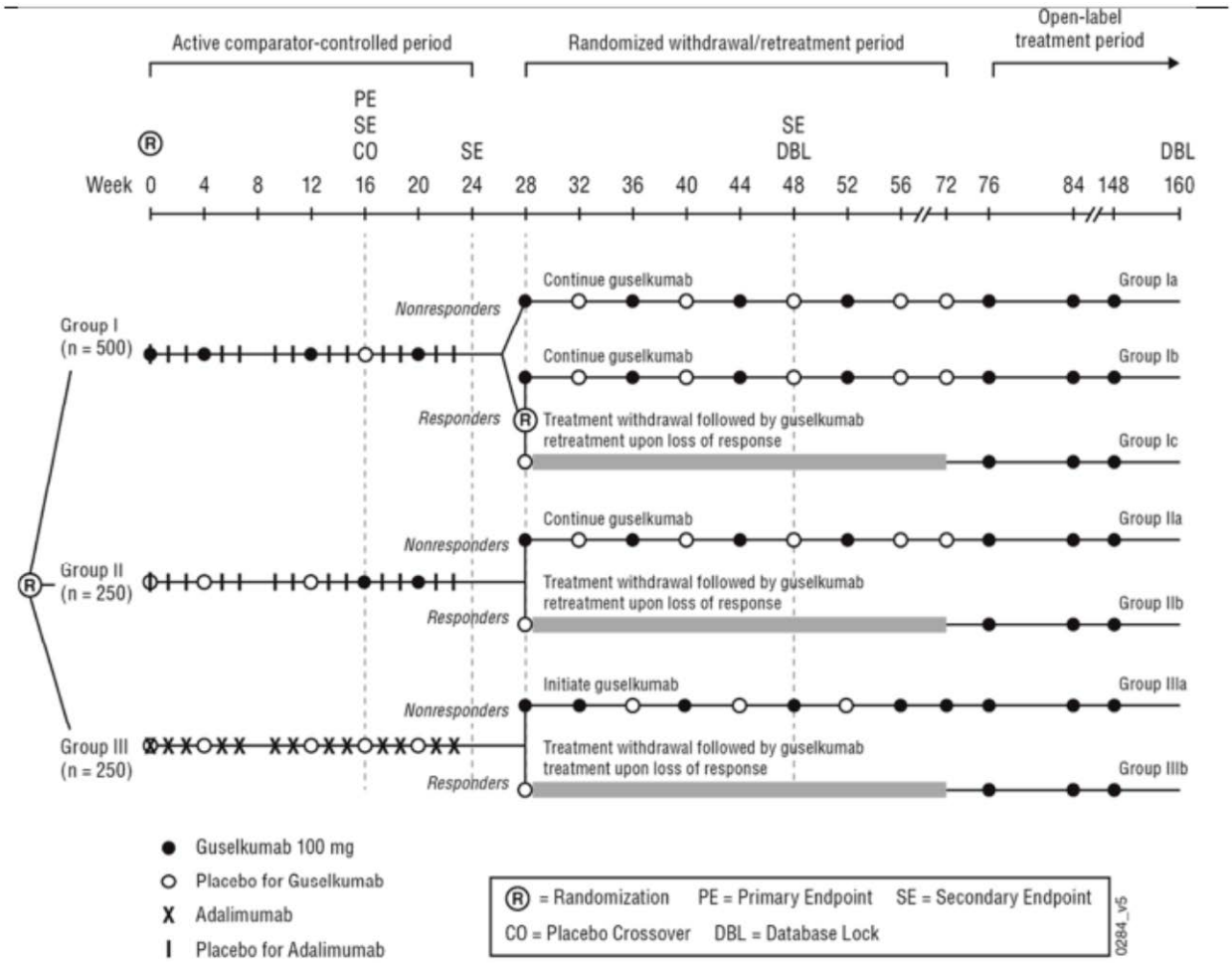
The open-label guselkumab treatment period began at Week 76 and continued through Week 160. Subjects received open-label guselkumab q8w through Week 148. A follow-up safety visit was scheduled at Week 160.

Database locks were planned for Weeks 48 and 160.

Figure 5 summarizes the study design.

Reference ID: 4084700

Figure 5. Study Design (3002)



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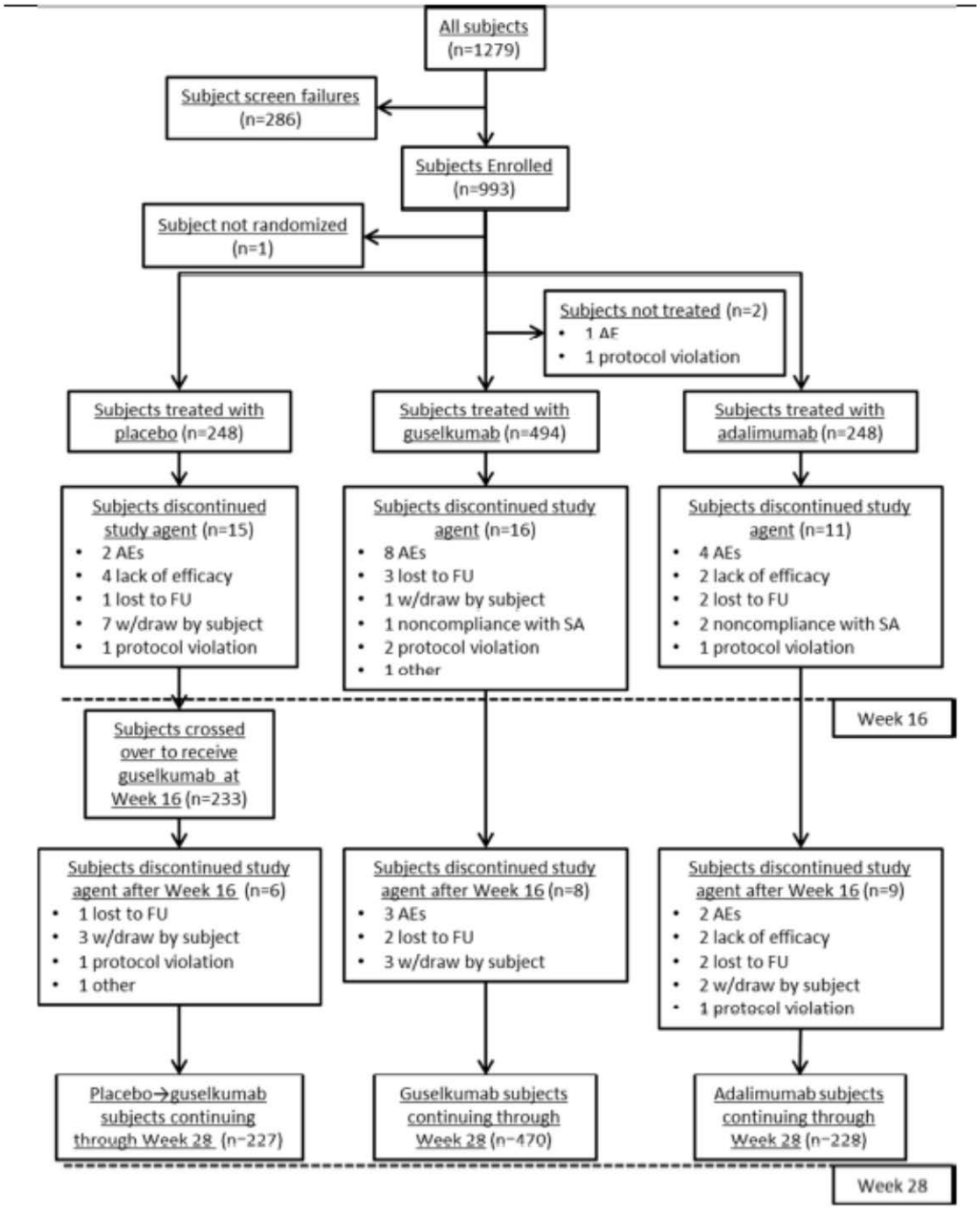
7.3.4. Disposition

A total of 993 subjects were enrolled in this study and 992 subjects were treated at Week 0, including 496 subjects in the guselkumab group, 248 subjects in the placebo group, and 248 subjects in the adalimumab group. Disposition is summarized in Figures 6 – 8.

Figure 6. Subject Disposition through Week 28 in Study 3002



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

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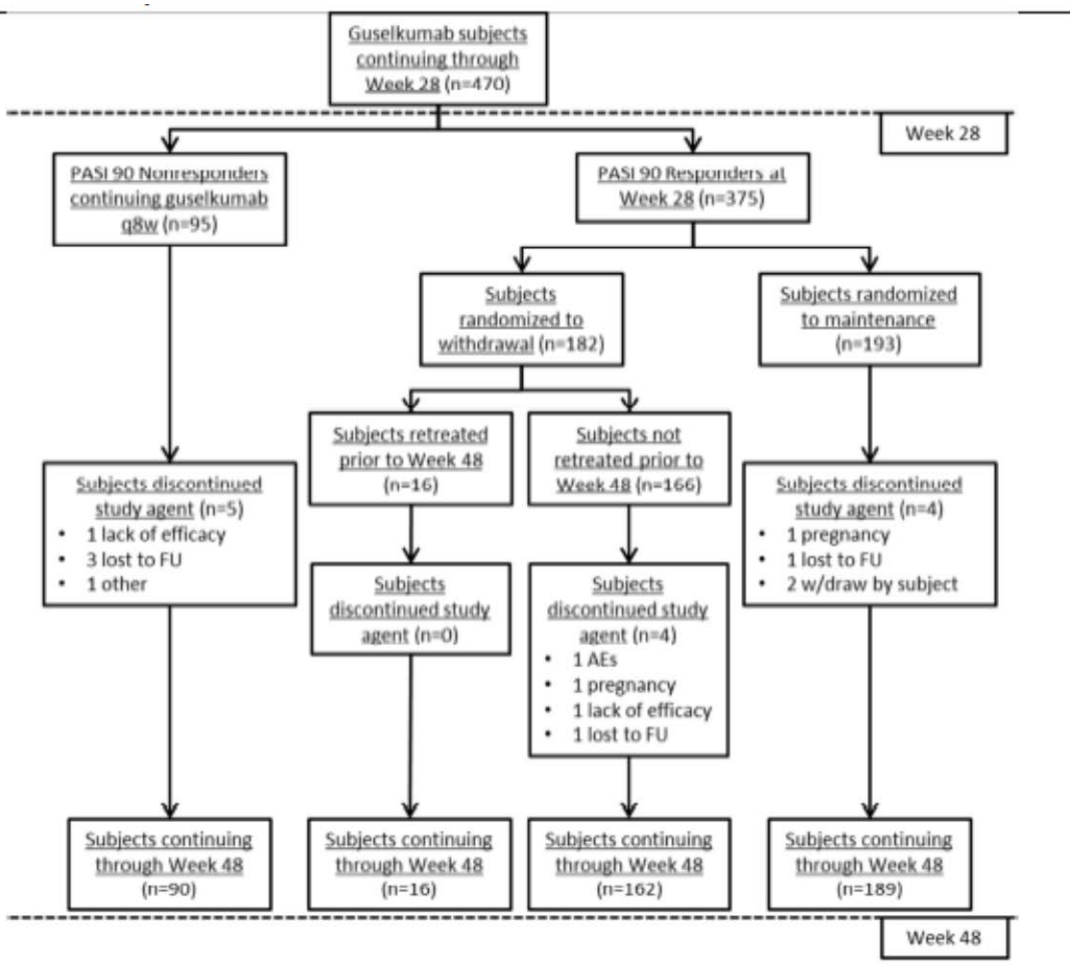
Figure 7. Subject Disposition from Week 28 through Week 48 for Subjects Rerandomized at Week 28 in Study 3002



Source: TSIDS01D.RTF, 16JUN2016, 18:39; TSIDS01E.RTF, 16JUN2016, 18:39; TSITG01C.RTF, 21JUN2016, 10:32; TSITG02A.RTF, 16JUN2016, 18:40; TSITG02B.RTF, 16JUN2016, 18:40; TSIDS02A.RTF, 16JUN2016, 18:39; TSIDS01C.RTF, 16JUN2016, 18:39

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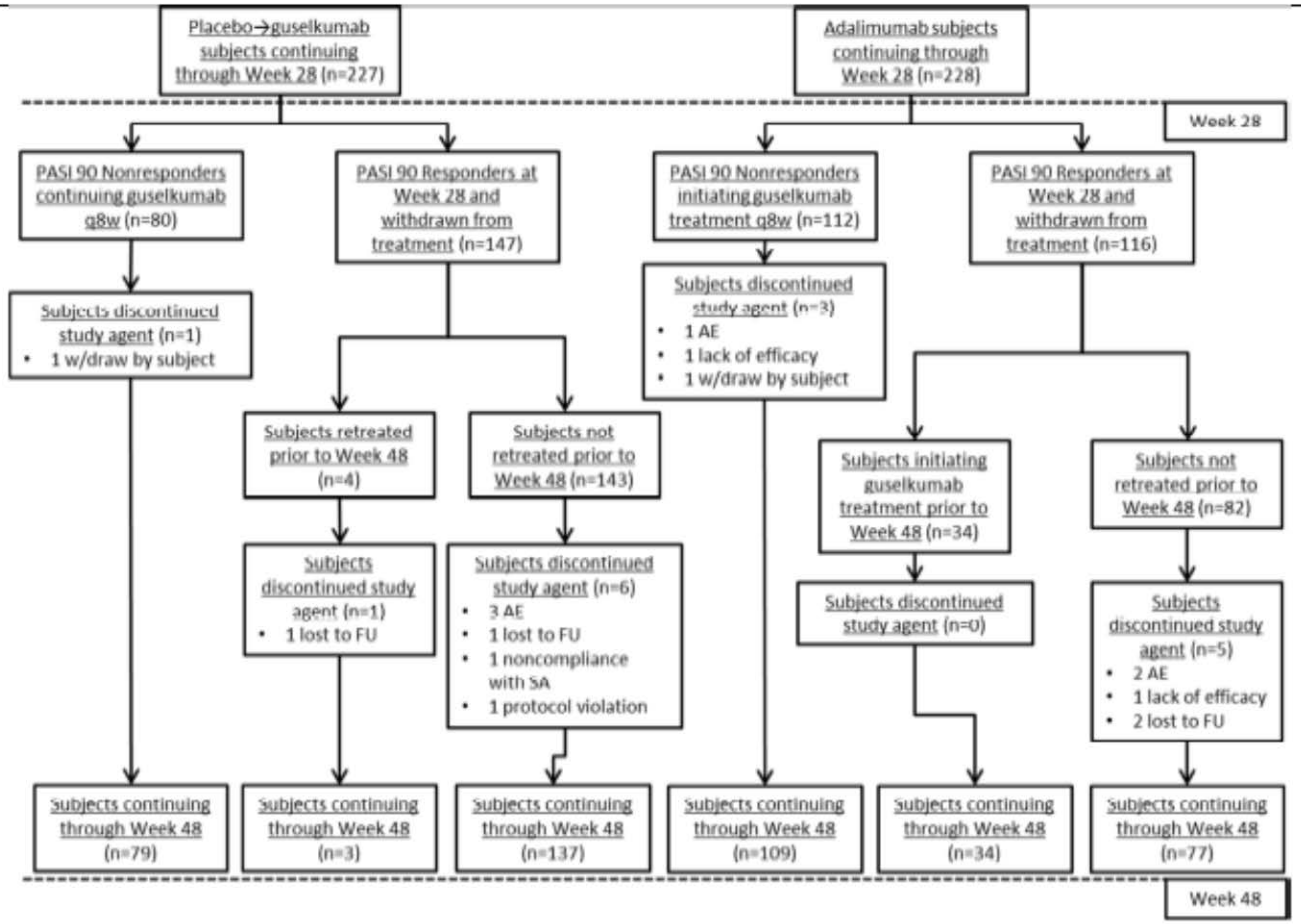
Figure 8. Subject Disposition from Week 28 through Week 48 for Subjects Not Rerandomized at Week 28 in Study 3002



Source: TSIDS01D.RTF, 16JUN2016, 18:39; TSIDS01E.RTF, 16JUN2016, 18:39; TSIDS02A.RTF, 16JUN2016, 18:39; TSITG01C.RTF, 21JUN2016, 10:32; TSITG02A.RTF, 16JUN2016, 18:40; TSIINFU01A.RTF, 16JUN2016, 18:39

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7.3.5. Demographic and Baseline Characteristics / Medical History

Clinical disease characteristics and CV medical history were similar between treatment groups at baseline.

TSIDEM01A: Summary of Demographics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3002)

	Placebo	Guselkumab	Adalimumab	Total
Analysis Set: Subjects randomized at Week 0	248	496	248	992
Age (years)				
N	248	496	248	992
Mean (SD)	43.3 (12.38)	43.7 (12.23)	43.2 (11.92)	43.5 (12.18)
Median	43.0	44.0	43.0	43.0
Range	(18; 71)	(18; 74)	(19; 70)	(18; 74)
IQ range	(35.0; 52.0)	(35.0; 53.0)	(35.0; 52.0)	(35.0; 52.0)
Sex				
N	248	496	248	992
Male	173 (69.8%)	349 (70.4%)	170 (68.5%)	692 (69.8%)
Female	75 (30.2%)	147 (29.6%)	78 (31.5%)	300 (30.2%)
Race				
N	248	496	248	992
White	206 (83.1%)	408 (82.3%)	200 (80.6%)	814 (82.1%)
Black or African American	8 (3.2%)	6 (1.2%)	5 (2.0%)	19 (1.9%)
Asian	27 (10.9%)	72 (14.5%)	37 (14.9%)	136 (13.7%)
American Indian or Alaska Native	1 (0.4%)	2 (0.4%)	2 (0.8%)	5 (0.5%)
Native Hawaiian or other Pacific Islander	1 (0.4%)	1 (0.2%)	1 (0.4%)	3 (0.3%)
Other	3 (1.2%)	5 (1.0%)	2 (0.8%)	10 (1.0%)
Multiple	2 (0.8%)	2 (0.4%)	1 (0.4%)	5 (0.5%)
Unknown	0	0	0	0
Not Reported	0	0	0	0
Ethnicity (Hispanic/Latino)				
N	248	496	248	992
Yes	12 (4.8%)	27 (5.4%)	13 (5.2%)	52 (5.2%)
No	234 (94.4%)	460 (92.7%)	233 (94.0%)	927 (93.4%)
Unknown	0	1 (0.2%)	0	1 (0.1%)
Not Reported	2 (0.8%)	8 (1.6%)	2 (0.8%)	12 (1.2%)
Weight (kg)				
N	248	496	247	991
Mean (SD)	88.6 (20.04)	89.2 (20.83)	87.6 (21.04)	88.7 (20.68)
Median	85.6	87.7	84.6	86.1
Range	(52; 163)	(45; 198)	(45; 175)	(45; 198)
IQ range	(73.4; 101.5)	(75.0; 99.8)	(73.7; 99.2)	(74.1; 100.0)
≤ 90 kg	141 (56.9%)	277 (55.8%)	153 (61.9%)	571 (57.6%)
> 90 kg	107 (43.1%)	219 (44.2%)	94 (38.1%)	420 (42.4%)
Height (cm)				
N	248	496	247	991
Mean (SD)	173.2 (10.26)	173.4 (9.32)	171.8 (9.81)	172.9 (9.70)
Median	173.0	174.0	172.0	173.0
Range	(127; 199)	(142; 206)	(140; 197)	(127; 206)
IQ range	(166.0; 180.5)	(167.7; 180.0)	(165.0; 178.0)	(167.0; 180.0)
BMI (kg/m^2)				
N	248	496	247	991
Mean (SD)	29.6 (6.56)	29.6 (6.45)	29.6 (6.56)	29.6 (6.50)

TSIDEM01A: Summary of Demographics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3002)				
	Placebo	Guselkumab	Adalimumab	Total
Median	28.4	28.5	28.3	28.4
Range	(18; 63)	(17; 66)	(16; 58)	(16; 66)
IQ range	(25.2; 33.4)	(25.5; 32.6)	(25.1; 33.1)	(25.2; 33.0)

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TSIDEM01B: Summary of Demographics at Baseline; Subjects Randomized at Week 28 (Study CNTO1959PSO3002)

	Placebo	Guselkumab
Analysis Set: Subjects randomized at Week 28	182	193
Age (years)		
N	182	193
Mean (SD)	42.4 (11.69)	44.9 (13.09)
Median	42.0	46.0
Range	(18; 69)	(18; 74)
IQ range	(34.0; 51.0)	(35.0; 54.0)
Sex		
N	182	193
Male	135 (74.2%)	122 (63.2%)
Female	47 (25.8%)	71 (36.8%)
Race		
N	182	193
White	156 (85.7%)	160 (82.9%)
Black or African American	1 (0.5%)	2 (1.0%)
Asian	22 (12.1%)	27 (14.0%)
American Indian or Alaska Native	0	1 (0.5%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0
Other	1 (0.5%)	2 (1.0%)
Multiple	1 (0.5%)	1 (0.5%)
Unknown	0	0
Not Reported	0	0
Ethnicity (Hispanic/Latino)		
N	182	193
Yes	8 (4.4%)	11 (5.7%)
No	171 (94.0%)	178 (92.2%)
Unknown	1 (0.5%)	0
Not Reported	2 (1.1%)	4 (2.1%)
Weight (kg)		
N	182	193
Mean (SD)	87.4 (20.67)	88.5 (20.31)
Median	85.4	85.7
Range	(52; 198)	(45; 151)
IQ range	(74.0; 97.0)	(75.0; 99.8)
≤ 90 kg	107 (58.8%)	114 (59.1%)
> 90 kg	75 (41.2%)	79 (40.9%)
Height (cm)		
N	182	193
Mean (SD)	174.1 (8.48)	172.5 (9.87)
Median	175.0	173.0
Range	(152; 192)	(147; 206)
IQ range	(168.8; 180.0)	(165.1; 180.0)
BMI (kg/m^2)		
N	182	193
Mean (SD)	28.8 (6.39)	29.7 (6.33)

Reference ID: 4084700

TSIDEM01B: Summary of Demographics at Baseline; Subjects Randomized at Week 28 (Study CNTO1959PSO3002)		
	Placebo	Guselkumab
Median	27.7	28.5
Range	(17; 66)	(18; 51)
IQ range	(24.7; 31.5)	(25.6; 32.9)

[TSIDEM01B.RTF] [CNTO1959\PSO3002\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM01B.SAS] 12AUG2016, 13:36

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TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3002)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects randomized at Week 0	248	496	248	992
Psoriasis disease duration (yrs)				
N	248	496	248	992
Mean (SD)	17.86 (11.875)	17.86 (11.994)	17.59 (11.654)	17.79 (11.869)
Median	17.00	16.00	15.00	16.00
Range	(0.7; 50.0)	(0.6; 60.0)	(0.4; 52.0)	(0.4; 60.0)
IQ range	(9.00; 25.00)	(8.00; 25.00)	(8.00; 25.00)	(8.00; 25.00)
Age at diagnosis (yrs)				
N	248	496	248	992
Mean (SD)	25.5 (12.93)	26.0 (13.32)	25.7 (13.26)	25.8 (13.20)
Median	24.0	24.0	24.0	24.0
Range	(0; 67)	(0; 69)	(0; 65)	(0; 69)
IQ range	(16.0; 33.0)	(16.0; 36.0)	(15.0; 34.5)	(16.0; 35.0)
Subjects with psoriatic arthritis at baseline	46 (18.5%)	89 (17.9%)	44 (17.7%)	179 (18.0%)
Subjects with scalp psoriasis at baseline	212 (85.5%)	423 (85.3%)	205 (82.7%)	840 (84.7%)
Subjects with nail psoriasis at baseline	139 (56.0%)	280 (56.5%)	139 (56.0%)	558 (56.3%)
Subjects with hand and/or foot psoriasis at baseline	67 (27.0%)	127 (25.6%)	62 (25.0%)	256 (25.8%)
BSA(%)				
N	248	496	248	992
Mean (SD)	28.0 (16.54)	28.5 (16.44)	29.1 (16.72)	28.5 (16.52)
Median	22.0	24.0	25.0	24.0
Range	(10; 89)	(10; 92)	(10; 86)	(10; 92)
IQ range	(15.0; 37.0)	(15.0; 36.0)	(17.0; 38.0)	(16.0; 37.0)
BSA				
N	248	496	248	992
≥ 20%	146 (58.9%)	318 (64.1%)	158 (63.7%)	622 (62.7%)
< 20%	102 (41.1%)	178 (35.9%)	90 (36.3%)	370 (37.3%)
PASI score (0-72)				
N	248	496	248	992
Mean (SD)	21.51 (7.965)	21.90 (8.812)	21.70 (8.957)	21.75 (8.638)
Median	18.95	19.20	19.00	19.00
Range	(12.0; 50.9)	(11.7; 64.9)	(11.7; 58.0)	(11.7; 64.9)
IQ range	(15.65; 25.20)	(15.30; 25.80)	(15.25; 25.70)	(15.35; 25.60)
PASI score				
N	248	496	248	992
≥ 20	109 (44.0%)	220 (44.4%)	110 (44.4%)	439 (44.3%)
< 20	139 (56.0%)	276 (55.6%)	138 (55.6%)	553 (55.7%)
IGA score				
N	248	496	248	992
Cleared (0)	0	0	0	0
Minimal (1)	0	0	0	0
Mild (2)	0	1 (0.2%)	0	1 (0.1%)
Moderate (3)	191 (77.0%)	380 (76.6%)	195 (78.6%)	766 (77.2%)
Severe (4)	57 (23.0%)	115 (23.2%)	53 (21.4%)	225 (22.7%)

Reference ID: 4084700

TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 0 (Study CNTO1959PSO3002)

	Placebo	Guselkumab	Adalimumab	Total
ss-IGA score				
N	212	423	205	840
Absence of disease (0)	0	0	0	0
Very mild (1)	10 (4.7%)	15 (3.5%)	11 (5.4%)	36 (4.3%)
Mild (2)	33 (15.6%)	80 (18.9%)	43 (21.0%)	156 (18.6%)
Moderate (3)	133 (62.7%)	267 (63.1%)	118 (57.6%)	518 (61.7%)
Severe (4)	36 (17.0%)	61 (14.4%)	33 (16.1%)	130 (15.5%)
f-PGA score				
N	139	280	139	558
Cleared (0)	0	0	0	0
Minimal (1)	16 (11.5%)	34 (12.1%)	15 (10.8%)	65 (11.6%)
Mild (2)	40 (28.8%)	92 (32.9%)	51 (36.7%)	183 (32.8%)
Moderate (3)	65 (46.8%)	122 (43.6%)	59 (42.4%)	246 (44.1%)
Severe (4)	18 (12.9%)	32 (11.4%)	14 (10.1%)	64 (11.5%)
NAPSI score (0-8)				
N	140	280	140	560
Mean (SD)	5.0 (2.04)	4.8 (1.96)	4.5 (1.90)	4.7 (1.97)
Median	4.5	4.0	4.0	4.0
Range	(1; 8)	(1; 8)	(1; 8)	(1; 8)
IQ range	(4.0; 6.0)	(4.0; 6.0)	(3.0; 6.0)	(4.0; 6.0)
hf-PGA score				
N	67	127	62	256
Cleared (0)	0	0	0	0
Almost Cleared (1)	4 (6.0%)	13 (10.2%)	6 (9.7%)	23 (9.0%)
Mild (2)	23 (34.3%)	43 (33.9%)	17 (27.4%)	83 (32.4%)
Moderate (3)	35 (52.2%)	58 (45.7%)	32 (51.6%)	125 (48.8%)
Severe (4)	5 (7.5%)	13 (10.2%)	7 (11.3%)	25 (9.8%)

[TSIDEM02A.RTF] [CNTO1959\PSO3002\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM02A.SAS] 16JUN2016, 18:37

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TSIDEM02B: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 28 (Study CNTO1959PSO3002)

	Placebo	Guselkumab
Analysis set: Subjects randomized at Week 28	182	193
Psoriasis disease duration (yrs)		
N	182	193
Mean (SD)	17.63 (11.853)	18.78 (12.624)
Median	15.50	16.00
Range	(0.6; 56.0)	(1.1; 60.0)
IQ range	(8.00; 24.25)	(9.00; 25.00)
Age at diagnosis (yrs)		
N	182	193
Mean (SD)	24.9 (12.86)	26.2 (14.39)
Median	23.0	24.0
Range	(3; 69)	(0; 62)
IQ range	(15.0; 32.0)	(15.0; 37.0)
Subjects with psoriatic arthritis at baseline	33 (18.1%)	31 (16.1%)
Subjects with scalp psoriasis at baseline	162 (89.0%)	157 (81.3%)
Subjects with nail psoriasis at baseline	97 (53.3%)	108 (56.0%)
Subjects with hand and/or foot psoriasis at baseline	54 (29.7%)	46 (23.8%)
BSA(%)		
N	182	193
Mean (SD)	29.1 (15.43)	27.8 (16.40)
Median	25.5	22.0
Range	(10; 80)	(10; 90)
IQ range	(16.0; 36.0)	(15.0; 36.0)
BSA		
N	182	193
≥ 20%	123 (67.6%)	118 (61.1%)
< 20%	59 (32.4%)	75 (38.9%)
PASI score (0-72)		
N	182	193
Mean (SD)	22.36 (8.815)	21.72 (8.453)
Median	19.20	19.40
Range	(11.7; 54.1)	(12.0; 58.8)
IQ range	(15.60; 27.00)	(15.30; 25.80)
PASI score		
N	182	193
≥ 20	84 (46.2%)	86 (44.6%)
< 20	98 (53.8%)	107 (55.4%)
IGA score		
N	182	193
Cleared (0)	0	0
Minimal (1)	0	0
Mild (2)	0	0
Moderate (3)	136 (74.7%)	156 (80.8%)
Severe (4)	46 (25.3%)	37 (19.2%)

TSIDEM02B: Summary of Clinical Disease Characteristics at Baseline; Subjects Randomized at Week 28 (Study CNTO1959PSO3002)

	Placebo	Guselkumab
ss-IGA score		
N	162	157
Absence of disease (0)	0	0
Very mild (1)	6 (3.7%)	4 (2.5%)
Mild (2)	31 (19.1%)	28 (17.8%)
Moderate (3)	100 (61.7%)	100 (63.7%)
Severe (4)	25 (15.4%)	25 (15.9%)
f-PGA score		
N	97	108
Cleared (0)	0	0
Minimal (1)	10 (10.3%)	18 (16.7%)
Mild (2)	35 (36.1%)	37 (34.3%)
Moderate (3)	45 (46.4%)	42 (38.9%)
Severe (4)	7 (7.2%)	11 (10.2%)
NAPSI score (0-8)		
N	97	108
Mean (SD)	5.0 (2.05)	4.4 (1.83)
Median	5.0	4.0
Range	(1; 8)	(1; 8)
IQ range	(4.0; 6.0)	(3.0; 6.0)
hf-PGA score		
N	54	46
Cleared (0)	0	0
Almost Cleared (1)	3 (5.6%)	7 (15.2%)
Mild (2)	18 (33.3%)	14 (30.4%)
Moderate (3)	29 (53.7%)	22 (47.8%)
Severe (4)	4 (7.4%)	3 (6.5%)

[TSIDEM02B.RTF] [CNTO1959\PSO3002\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM02B.SAS] 16JUN2016, 18:37

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TSIDEM04A: Summary of Medical History and Current Diagnoses; Subjects Randomized at Week 0 (Study CNTO1959PSO3002)

	Placebo	Guselkumab	Adalimumab	Total
Analysis set: Subjects randomized at Week 0	248	496	248	992
Coronary Artery Disease	5 (2.0%)	13 (2.6%)	5 (2.0%)	23 (2.3%)
Myocardial Infarction	4 (1.6%)	6 (1.2%)	3 (1.2%)	13 (1.3%)
Angina pectoris	3 (1.2%)	1 (0.2%)	2 (0.8%)	6 (0.6%)
Coronary artery bypass graft	2 (0.8%)	3 (0.6%)	2 (0.8%)	7 (0.7%)
Percutaneous coronary intervention	3 (1.2%)	4 (0.8%)	1 (0.4%)	8 (0.8%)
Peripheral vascular disease	1 (0.4%)	2 (0.4%)	0	3 (0.3%)
Transient ischemic attack	1 (0.4%)	1 (0.2%)	0	2 (0.2%)
Stroke	0	1 (0.2%)	1 (0.4%)	2 (0.2%)
Diabetes mellitus	22 (8.9%)	50 (10.1%)	21 (8.5%)	93 (9.4%)
Hyperlipidemia	34 (13.7%)	71 (14.3%)	33 (13.3%)	138 (13.9%)
Hypertension	64 (25.8%)	147 (29.6%)	58 (23.4%)	269 (27.1%)
Use of Cigarettes				
Current or former smoker	121 (48.8%)	252 (50.8%)	132 (53.2%)	505 (50.9%)
Current smoker	86 (34.7%)	157 (31.7%)	86 (34.7%)	329 (33.2%)
Never used	127 (51.2%)	244 (49.2%)	116 (46.8%)	487 (49.1%)
Smoking pack years				
N	121	250	132	503
Mean (SD)	15.88 (14.675)	18.57 (19.990)	14.51 (11.912)	16.86 (17.025)
Median	11.58	13.00	10.36	12.00
Range	(0.0; 88.7)	(0.0; 150.7)	(0.5; 50.1)	(0.0; 150.7)
IQ range	(6.17; 21.15)	(5.07; 23.27)	(5.04; 21.77)	(5.13; 22.40)
Family history of early coronary artery disease (< 55 years of age)	19 (7.7%)	40 (8.1%)	16 (6.5%)	75 (7.6%)
Asthma	12 (4.8%)	27 (5.4%)	7 (2.8%)	46 (4.6%)
Depression	18 (7.3%)	38 (7.7%)	19 (7.7%)	75 (7.6%)
Chronic liver disease	3 (1.2%)	9 (1.8%)	4 (1.6%)	16 (1.6%)
Hospitalized within past year (excluding pregnancy)	26 (10.5%)	27 (5.4%)	16 (6.5%)	69 (7.0%)
Hospitalized within the past year for infection	3 (1.2%)	2 (0.4%)	1 (0.4%)	6 (0.6%)
Skin Squamous Cell Carcinoma (SCC)	0	0	0	0
Skin Basal Cell Carcinoma (BCC)	3 (1.2%)	2 (0.4%)	1 (0.4%)	6 (0.6%)
Other malignancy	3 (1.2%)	7 (1.4%)	3 (1.2%)	13 (1.3%)
Family history of cancer in a 1st degree relative (excluding Skin squamous cell carcinoma and Skin basal cell carcinoma)	36 (14.5%)	94 (19.0%)	44 (17.7%)	174 (17.5%)
Use of Alcohol				
Current or former user	159 (64.1%)	325 (65.5%)	167 (67.3%)	651 (65.6%)
Current alcohol user	141 (56.9%)	301 (60.7%)	155 (62.5%)	597 (60.2%)
Never used	89 (35.9%)	171 (34.5%)	81 (32.7%)	341 (34.4%)

[TSIDEM04A.RTF] [CNTO1959\PSO3002\DBR_WEEK_048\RE_WEEK_048_CSR\PROD\TSIDEM04A.SAS] 16JUN2016, 18:38

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7.3.6. CEC-Adjudicated Cardiovascular Events

CEC-adjudicated cardiovascular events are summarized in Tables 7 through 9.

Table 7. Study 3002: CEC-Adjudicated Cardiovascular Events (Through Week 48)

	Adalimumab (US)*	Adalimumab (EU)	Placebo[a]	Continuous Guselkumab[b] 100 mg	Overall Guselkumab[c] 100 mg
# of subjects treated	81	167	248	312	727
Total subject-years of follow-up	43	88	76	273	582**
MACE					
# of Events (%)	1 (1.23)	0	0	3 (0.96)	4 (0.55)
100 Subject-years	2.33	0	0	1.10	0.69
CV death					
# of Events (%)	0	0	0	0	0
100 Subject-years	0	0	0	0	0
Nonfatal MI					
# of Events (%)	1 (1.23)	0	0	3 (0.96)	4 (0.55)
100 Subject-years	2.33	0	0	1.10	0.69
Nonfatal Stroke					
# of Events (%)	0	0	0	0	0
100 Subject-years	0	0	0	0	0
All-Cause Mortality					
# of Events (%)	0	0	0	0	0
100 Subject-years	0	0	0	0	0
Other CV Events					
# of Events (%)	1 (1.23)			1 (0.32)	2 (0.28)
100 Subject-years	2.33			0.37	0.34
Hospitalization for Unstable Angina					
# of Events (%)	0	0	0	0	1 (0.14)
100 Subject-years	0	0	0	0	0.17
Heart Failure					
# of Events (%)	1 (1.23)	0	0	1 (0.32)	0
100 Subject-years	2.33	0	0	0.37	0

CABG: coronary artery bypass graft surgery; EU: European Union-approved adalimumab; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction; PCI: percutaneous coronary intervention
*The US-licensed adalimumab group includes US and Canadian subjects.

****Differs from applicant's results**
[a]Includes data during the placebo period for subjects who were randomized to placebo at Week 0
[b]Includes data (Week 0 through Week 48) for subjects who were randomized to guselkumab at Week 0 and were either PASI 90 nonresponders at Week 28 or PASI 90 responders at Week 28 who were randomized to continue guselkumab at Week 28
[c]Includes the following data:
(1) data (Week 0 through Week 48) for subjects who were randomized to guselkumab at Week 0 and were either PASI 90 nonresponders at Week 28 or PASI 90 responders at Week 28 who were randomized to continue to receive guselkumab at Week 28
(2) data (Week 0 through Week 28 and from start of retreatment after loss of response to Week 48) for subjects who were randomized to guselkumab at Week 0 and were PASI 90 responders at Week 28 and were randomized to the withdrawal group at Week 28
(3) data (Week 16 through Week 48) for subjects who were randomized to placebo at Week 0 and crossed over to guselkumab 100 mg at Week 16 and were PASI 90 nonresponders at Week 28 and continue to receive guselkumab
(4) data (Week 16 through Week 28 and from start of retreatment after loss of response to Week 48) for subjects who were randomized to placebo at Week 0 and crossed over to guselkumab 100 mg at Week 16 and were PASI 90 responders at Week 28 and were withdrawn from guselkumab at Week 28

Analysis by Ruquan Liu, MD, MS (Division of Biometrics 1)

Table 8. Study 3002: CEC-Adjudicated Treatment Emergent Cardiovascular Events (Through Week 48)

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category[a]	CEC Detailed Event Type[a]	Serious (Y/N)[b]	Reviewer Category and Comments
1	Placebo to Guselkumab 100 mg at Week 16 (Withdrawal at Week 28)	CNTO1959PSO3002-RU00378-20580 39 yo white female (Russia)	Guselkumab (withdrawal)	141	(b) (6)	303	AMI (ISCHEMIC HEART DISEASE. ACUTE MYOCARDIAL INFARCTION)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (Anterior STEMI) (history of HLP, smoking, and suboptimal weight profile)
2	Guselkumab 100 mg	CNTO1959PSO3002-CA00249-21024 52 yo white male (Canada)	Guselkumab	141	(b) (6)	193	Myocardial ischaemia (ISCHEMIC CORONARY EVENT)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (NSTEMI) (history of HLP)
3		CNTO1959PSO3002-PL00240-20308 56 yo white male (Poland)	Guselkumab	141	(b) (6)	166	Myocardial infarction (MYOCARDIAL INFARCTION)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (Inferior STEMI) (history of CAD, HLP, and smoking)
4		CNTO1959PSO3002-US91507-20944 67 yo white male (US)	Guselkumab	29	(b) (6)	37	Hypertension (WORSENING OF HYPERTENSION)	HUA		N	Nonfatal MI (AMI – STEMI, requiring urgent CABG) (family history of premature CAD; history of asthma)
5		CNTO1959PSO3002-ES00532-20843 64 yo white female (Spain)	Guselkumab	88	(b) (6)	127	Cardiac failure (HEART FAILURE)	HF	HF Hospitaliza-tion	Y	Heart failure due to atrial fibrillation with a rapid ventricular response (history of CAD, depression, DM,

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category[a]	CEC Detailed Event Type[a]	Serious (Y/N)[b]	Reviewer Category and Comments
											hyperlipidemia, prior MI, and prior PCI)
6		CNTO1959PSO3002-PL00244-20899 64 yo white female (Poland)	Guselkumab	24	(b) (6)	36	Angina unstable (UNSTABLE ANGINA PECTORIS)	HUA		Y	HUA (family history of premature CAD, history of DM and hyperlipidemia)
7	Adalimumab	CNTO1959PSO3002-US02138-20926 67 yo Native Hawaiian or Other Pacific Islander (USA)	Adalimumab	162	(b) (6)	213	Cardiac failure congestive (CONGESTIVE HEART FAILURE)	HF	Urgent HF Visit		Urgent HF Visit (history of DM and HTN)
8	Adalimumab to Guselkumab 100 mg	CNTO1959PSO3002-US92404-20995 56 yo white male (USA)	Adalimumab	1	(b) (6)	5	Myocardial infarction (MYOCARDIAL INFARCTION)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (Anterior STEMI) (history of AP, CAD, HLP, HTN, prior MI, family history of premature CAD, and suboptimal weight profile)

AMI: acute myocardial infarction; AP: angina pectoris; CABG: Coronary artery bypass graft surgery; CAD: coronary artery disease; CV: cardiovascular; DM: diabetes mellitus; HF: heart failure; HLP: hyperlipidemia; HTN: hypertension; HUA: Hospitalization for unstable angina; MI: myocardial infarction; N: no; NSTEMI: non-ST-segment elevation MI; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation MI; Y: yes; yo: year old.
[a]Determined by Clinical Events Committee (CEC)
[b]Adjudicated Cardiovascular (CV) Events include serious and nonserious events
Adapted from Sponsor. Response to Information Request dated March 24, 2017.

Table 9. Study 3002: CEC-Adjudicated Cardiovascular Events (Through Week 48)

	Adalimumab	Placebo to Guselkumab	Guselkumab	Adalimumab to Guselkumab
# of subjects treated	248	233	494	146
Total subject-years of follow-up	131	73	442	88
MACE				
# of Events (%)	0	1 (0.43)	3 (0.61)	1 (0.68)
100 Subject-years	0	1.37	0.68	1.14
CV death				
# of Events (%)	0	0	0	0
100 Subject-years	0	0	0	0
Nonfatal MI				
# of Events (%)		1 (0.43)	3 (0.61)	1 (0.68)
100 Subject-years		1.37	0.68	1.14
Nonfatal Stroke				
# of Events (%)				
100 Subject-years				
All-Cause Mortality				
# of Events (%)	0	0	0	0
100 Subject-years	0	0	0	0
Other CV Events				
# of Events (%)	1 (0.40)		2 (0.40)0	0
100 Subject-years	0.76		0.45	0
Hospitalization for Unstable Angina				
# of Events (%)	0		1 (0.20)	0
100 Subject-years	0		0.23	0
Heart Failure				
# of Events (%)	1 (0.40)	0	1 (0.20)	0
100 Subject-years	0.76	0	0.23	0

CV: cardiovascular; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction
Analysis by Ruquan Liu, MD, MS (Division of Biometrics 1)

7.4. Study 3003

Study 3003 was a phase 3, randomized, double-blind, multicenter study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis and an inadequate (IGA ≥ 2) response to ustekinumab at Week 16.

7.4.1. Key Inclusion Criteria

Inclusion criteria were similar to Study 2001.

7.4.2. Key Exclusion Criteria

Exclusion criteria were similar to Study 2001.

7.4.3. Treatment Groups and Study Design

The study consisted of 3 phases:

- Open-label phase (Week 0 to Week 16)
- Blinded active treatment phase (Week 16 through Week 44)
- Follow-up phase (Week 44 through Week 60)

Eligible subjects received open-label ustekinumab at Weeks 0 and 4. At week 16, efficacy was assessed using IGA which determined their subsequent treatment through Week 44.

- Subjects with an IGA ≥ 2 (mild to severe disease, i.e., subjects with an inadequate response to ustekinumab) were randomized in a 1:1 fashion to either
  - Guselkumab 100 mg at Weeks 16 and 20, then every 8 weeks (q8w) thereafter (i.e., weeks 28, 36, 44)
  - Ustekinumab q 12w (i.e., weeks 16, 28, and 40)
- Subjects with an IGA = 0 or 1 (cleared or minimal disease) continued to receive open-label ustekinumab q12w from Week 16 through Week 40.

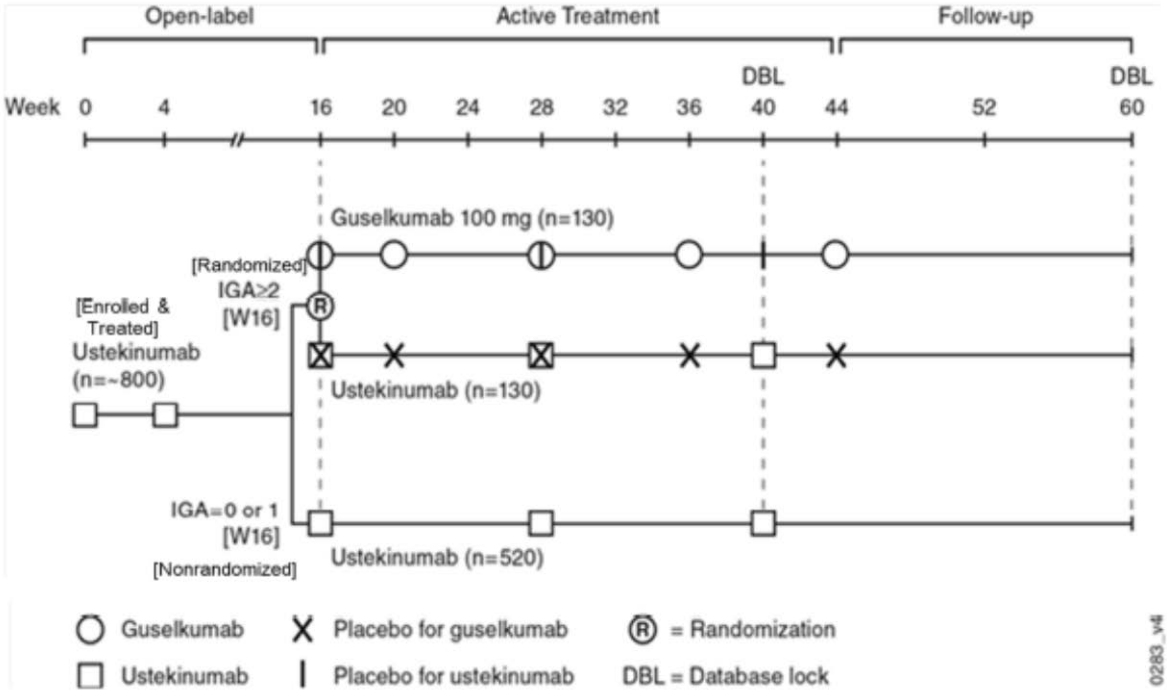
All subjects returned for a follow-up visit at Week 52 and a final safety visit at Week 60.

Database locks were planned for Weeks 40 and 60.

Figure 9 summarizes the study design.

Reference ID: 4084700

Figure 9. Study Design (3003)



Key: IGA=Investigator's Global Assessment; W=week.

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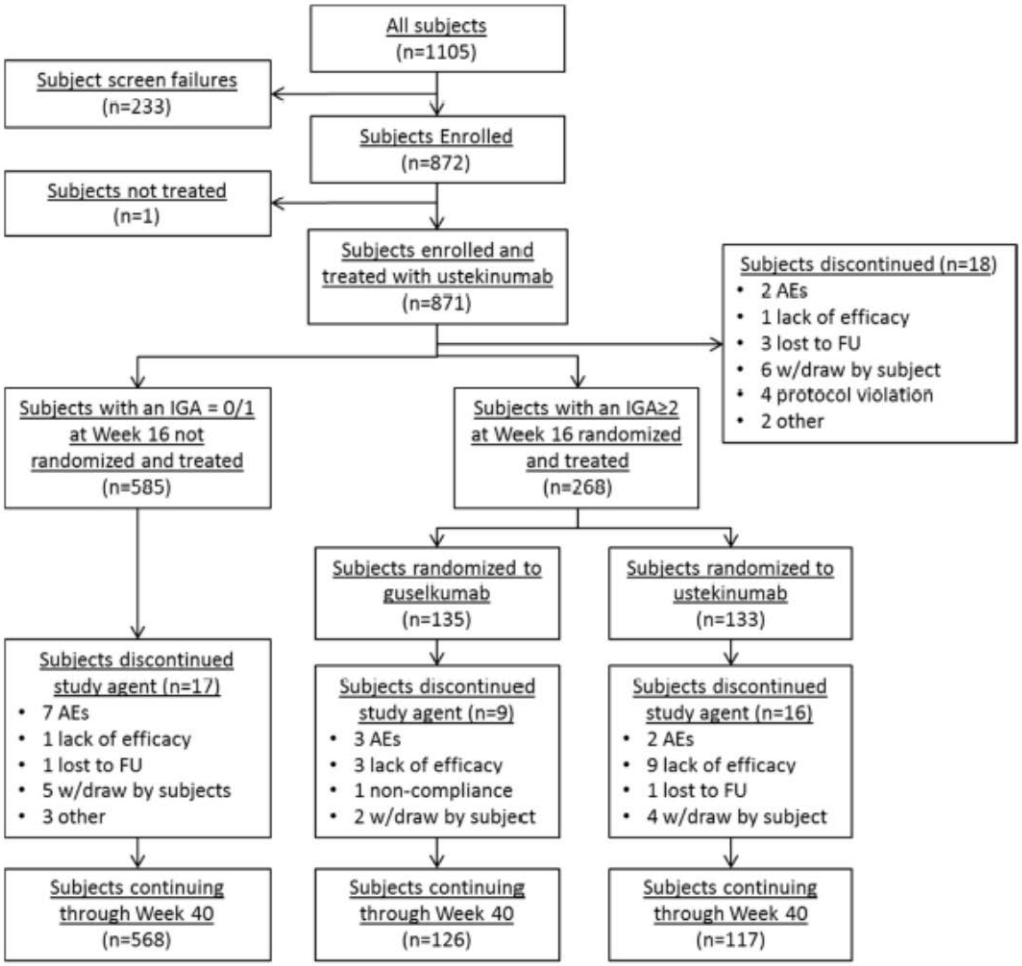
7.4.4. Disposition

A total of 1,105 subjects were screened, 872 subjects were randomized, and 871 subjects were treated with open-label ustekinumab 45 mg or 90 mg, according to the subject's baseline weight at Week 0. Subject disposition is summarized in Figure 10.

Figure 10. Subject Disposition (Study 3003)



Key: AEs=adverse events; FU=follow-up; IGA=Investigator's Global Assessment; w/draw=withdrawal

Extracted from: TSITG01 (n=1105, 233); TSITG02 (n=872, 871); TSIDS01a (n=9/135, 16/133, 268); TSIDS01c (n=17/585); LSIDS01 (n=18); LSIDS03 (n=135; n=133); LSIDS07 (n=1).

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7.4.5. Demographics and Baseline Characteristics / Medical History

Hypertension (25.6%) and hyperlipidemia (12.9%) were the most common medical history diagnoses for the enrolled and treated subjects. A higher percentage of randomized subjects had diabetes in the ustekinumab treatment group (11.3%), compared to the guselkumab treatment group (3%).

TSIDEM01B: Summary of Demographics at Baseline; Enrolled and Treated Subjects CNTO1959PSO3003)

	Ustekinumab
Analysis set: enrolled and treated subjects	871
Age (years)	
N	871
Mean (SD)	43.1 (13.21)
Median	42.0
Range	(18; 84)
IQ range	(33.0; 53.0)
Sex	
N	871
Male	566 (65.0%)
Female	305 (35.0%)
Race	
N	871
White	747 (85.8%)
Black or African American	13 (1.5%)
Asian	103 (11.8%)
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	2 (0.2%)
Other	2 (0.2%)
Multiple	1 (0.1%)
Unknown	2 (0.2%)
Not Reported	1 (0.1%)
Ethnicity	
N	871
Hispanic or Latino	60 (6.9%)
Not Hispanic or Latino	796 (91.4%)
Unknown	4 (0.5%)
Not reported	11 (1.3%)
Weight (kg)	
N	871
Mean (SD)	88.3 (21.96)
Median	86.2
Range	(43; 189)
IQ range	(73.0; 101.0)
>100kg	231 (26.5%)
≤100kg	640 (73.5%)
Height (cm)	
N	871
Mean (SD)	172.3 (9.67)
Median	172.7
Range	(142; 205)
IQ range	(165.1; 179.5)
BMI (kg/m^2)	
N	871
Mean (SD)	29.7 (6.96)
Median	28.7
Range	(17; 65)
IQ range	(24.9; 32.8)

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TSIDEM01A: Summary of Demographics at Baseline; Randomized Subjects (Study CNTO1959PSO3003)

	Guselkumab	Ustekinumab	Total
Analysis set: randomized subjects	135	133	268
Age (years)			
N	135	133	268
Mean (SD)	44.2 (13.38)	43.0 (13.74)	43.6 (13.55)
Median	42.0	42.0	42.0
Range	(19; 74)	(20; 78)	(19; 78)
IQ range	(34.0; 55.0)	(32.0; 54.0)	(33.0; 54.0)
Sex			
N	135	133	268
Male	95 (70.4%)	88 (66.2%)	183 (68.3%)
Female	40 (29.6%)	45 (33.8%)	85 (31.7%)
Race			
N	135	133	268
White	109 (80.7%)	99 (74.4%)	208 (77.6%)
Black or African American	3 (2.2%)	3 (2.3%)	6 (2.2%)
Asian	22 (16.3%)	27 (20.3%)	49 (18.3%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	2 (1.5%)	2 (0.7%)
Other	1 (0.7%)	0	1 (0.4%)
Multiple	0	1 (0.8%)	1 (0.4%)
Unknown	0	0	0
Not Reported	0	1 (0.8%)	1 (0.4%)
Ethnicity			
N	135	133	268
Hispanic or Latino	9 (6.7%)	11 (8.3%)	20 (7.5%)
Not Hispanic or Latino	123 (91.1%)	119 (89.5%)	242 (90.3%)
Unknown	1 (0.7%)	1 (0.8%)	2 (0.7%)
Not reported	2 (1.5%)	2 (1.5%)	4 (1.5%)
Weight (kg)			
N	135	133	268
Mean (SD)	90.3 (22.15)	91.3 (25.84)	90.8 (24.01)
Median	89.0	88.4	89.0
Range	(43; 181)	(44; 189)	(43; 189)
IQ range	(76.4; 101.0)	(75.0; 101.8)	(75.3; 101.6)
>100kg	37 (27.4%)	37 (27.8%)	74 (27.6%)
≤100kg	98 (72.6%)	96 (72.2%)	194 (72.4%)
Height (cm)			
N	135	133	268
Mean (SD)	172.8 (9.55)	171.7 (10.00)	172.2 (9.78)
Median	173.0	172.0	172.9
Range	(145; 198)	(152; 196)	(145; 198)
IQ range	(166.0; 180.0)	(165.0; 178.0)	(166.0; 180.0)

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TSIDEM01C: Summary of Demographics at Baseline; Non-randomized and Continued to Receive Open-Label Treatment Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Analysis set: non-randomized and continued to receive open-label treatment subjects	585
Age (years)	
N	585
Mean (SD)	42.9 (13.05)
Median	42.0
Range	(18; 84)
IQ range	(33.0; 52.0)
Sex	
N	585
Male	372 (63.6%)
Female	213 (36.4%)
Race	
N	585
White	523 (89.4%)
Black or African American	7 (1.2%)
Asian	52 (8.9%)
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0
Other	1 (0.2%)
Multiple	0
Unknown	2 (0.3%)
Not Reported	0
Ethnicity	
N	585
Hispanic or Latino	38 (6.5%)
Not Hispanic or Latino	538 (92.0%)
Unknown	2 (0.3%)
Not reported	7 (1.2%)
Weight (kg)	
N	585
Mean (SD)	86.8 (20.63)
Median	86.0
Range	(46; 177)
IQ range	(71.4; 100.2)
>100kg	149 (25.5%)
≤100kg	436 (74.5%)
Height (cm)	
N	585
Mean (SD)	172.4 (9.61)
Median	172.7
Range	(142; 205)
IQ range	(165.1; 179.0)
BMI (kg/m^2)	
N	585
Mean (SD)	29.1 (6.36)
Median	28.0
Range	(17; 55)
IQ range	(24.7; 32.5)

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TSIDEM02B: Summary of Clinical Disease Characteristics at Baseline; Enrolled and Treated Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Analysis set: enrolled and treated subjects	871
Psoriasis disease duration (yrs)	
N	871
Mean (SD)	16.76 (12.197)
Median	14.00
Range	(0.4; 71.1)
IQ range	(7.00; 24.00)
Age at diagnosis (yrs)	
N	871
Mean (SD)	26.5 (14.00)
Median	23.0
Range	(0; 77)
IQ range	(16.0; 35.0)
Psoriatic arthritis	
N	871
Yes	128 (14.7%)
No	743 (85.3%)
BSA (%)	
N	871
Mean (SD)	28.2 (16.76)
Median	23.0
Range	(10; 95)
IQ range	(15.0; 35.0)
≥ 20%	532 (61.1%)
< 20%	339 (38.9%)
PASI score (0-72)	
N	871
Mean (SD)	21.61 (9.237)
Median	18.60
Range	(12.0; 64.4)
IQ range	(15.30; 24.70)
≥ 20	360 (41.3%)
< 20	511 (58.7%)
IGA score	
N	871
Cleared (0)	0
Minimal (1)	0
Mild (2)	1 (0.1%)
Moderate (3)	694 (79.7%)
Severe (4)	176 (20.2%)
DLQI (0-30)	
N	866
Mean (SD)	14.5 (7.18)
Median	14.0
Range	(0; 30)
IQ range	(9.0; 20.0)
PSSD sign score (0-100)	
N	866

TSIDEM02B: Summary of Clinical Disease Characteristics at Baseline; Enrolled and Treated Subjects (Study CNTO1959PSO3003)	
	Ustekinumab
Mean (SD)	60.7 (20.42)
Median	62.0
Range	(3; 100)
IQ range	(48.0; 77.0)
PSSD symptom score (0-100)	
N	866
Mean (SD)	50.6 (24.68)
Median	50.0
Range	(0; 100)
IQ range	(32.0; 70.0)

[TSIDEM02B.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEM02B.SAS] 28MAR2016, 14:25

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TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Randomized Subjects (Study CNTO1959PSO3003)

	Guselkumab	Ustekinumab	Total
Analysis set: randomized subjects	135	133	268
Psoriasis disease duration (yrs)			
N	135	133	268
Mean (SD)	18.20 (12.714)	15.62 (10.931)	16.92 (11.911)
Median	16.00	13.83	15.00
Range	(0.5; 53.0)	(0.6; 54.0)	(0.5; 54.0)
IQ range	(7.00; 25.00)	(7.93; 22.00)	(7.00; 23.53)
Age at diagnosis (yrs)			
N	135	133	268
Mean (SD)	26.1 (15.09)	27.5 (14.13)	26.8 (14.61)
Median	22.0	25.0	23.0
Range	(1; 73)	(3; 72)	(1; 73)
IQ range	(16.0; 34.0)	(16.0; 37.0)	(16.0; 35.0)
Psoriatic arthritis			
N	135	133	268
Yes	28 (20.7%)	21 (15.8%)	49 (18.3%)
No	107 (79.3%)	112 (84.2%)	219 (81.7%)
BSA (%)			
N	135	133	268
Mean (SD)	31.5 (19.80)	30.5 (17.86)	31.0 (18.84)
Median	25.0	24.0	25.0
Range	(10; 90)	(10; 83)	(10; 90)
IQ range	(16.0; 39.0)	(16.0; 40.0)	(16.0; 40.0)
≥ 20%	91 (67.4%)	80 (60.2%)	171 (63.8%)
< 20%	44 (32.6%)	53 (39.8%)	97 (36.2%)
PASI score (0-72)			
N	135	133	268
Mean (SD)	22.59 (9.300)	22.83 (9.393)	22.71 (9.330)
Median	19.10	19.40	19.30
Range	(12.0; 49.0)	(12.0; 53.7)	(12.0; 53.7)
IQ range	(15.80; 27.20)	(16.10; 27.40)	(15.90; 27.35)
≥ 20	61 (45.2%)	62 (46.6%)	123 (45.9%)
< 20	74 (54.8%)	71 (53.4%)	145 (54.1%)
IGA score			
N	135	133	268
Cleared (0)	0	0	0
Minimal (1)	0	0	0
Mild (2)	0	0	0
Moderate (3)	103 (76.3%)	100 (75.2%)	203 (75.7%)
Severe (4)	32 (23.7%)	33 (24.8%)	65 (24.3%)
DLQI (0-30)			
N	133	132	265
Mean (SD)	15.5 (7.94)	14.4 (6.68)	14.9 (7.35)
Median	15.0	14.5	15.0
Range	(0; 30)	(1; 28)	(0; 30)
IQ range	(9.0; 23.0)	(9.0; 20.0)	(9.0; 20.0)
PSSD sign score (0-100)			
N	133	132	265

Reference ID: 4084700

TSIDEM02A: Summary of Clinical Disease Characteristics at Baseline; Randomized Subjects (Study CNTO1959PSO3003)

	Guselkumab	Ustekinumab	Total
Mean (SD)	64.9 (20.31)	63.7 (20.77)	64.3 (20.51)
Median	65.0	63.0	65.0
Range	(12; 100)	(10; 100)	(10; 100)
IQ range	(53.0; 80.0)	(51.0; 80.0)	(52.0; 80.0)
PSSD symptom score (0-100)			
N	133	132	265
Mean (SD)	55.7 (25.50)	52.9 (25.58)	54.3 (25.53)
Median	58.0	52.0	54.0
Range	(0; 100)	(6; 100)	(0; 100)
IQ range	(34.0; 76.0)	(34.0; 73.0)	(34.0; 74.0)

[TSIDEM02A.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEM02A.SAS] 28MAR2016, 14:24

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TSIDEM02C: Summary of Clinical Disease Characteristics at Baseline; Non-randomized and Continued to Receive Open-Label Treatment Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Analysis set: non-randomized and continued to receive open-label treatment subjects	585
Psoriasis disease duration (yrs)	
N	585
Mean (SD)	16.69 (12.337)
Median	14.00
Range	(0.4; 71.1)
IQ range	(7.00; 24.42)
Age at diagnosis (yrs)	
N	585
Mean (SD)	26.4 (13.76)
Median	23.0
Range	(0; 77)
IQ range	(17.0; 35.0)
Psoriatic arthritis	
N	585
Yes	77 (13.2%)
No	508 (86.8%)
BSA (%)	
N	585
Mean (SD)	26.8 (15.61)
Median	22.0
Range	(10; 95)
IQ range	(15.0; 33.0)
≥ 20%	347 (59.3%)
< 20%	238 (40.7%)
PASI score (0-72)	
N	585
Mean (SD)	21.12 (9.199)
Median	18.00
Range	(12.0; 64.4)
IQ range	(15.30; 23.40)
≥ 20	227 (38.8%)
< 20	358 (61.2%)
IGA score	
N	585
Cleared (0)	0
Minimal (1)	0
Mild (2)	0
Moderate (3)	477 (81.5%)
Severe (4)	108 (18.5%)
DLQI (0-30)	
N	584
Mean (SD)	14.2 (7.09)
Median	14.0
Range	(0; 30)
IQ range	(9.0; 19.0)
PSSD sign score (0-100)	
N	584

Reference ID: 4084700

TSIDEM02C: Summary of Clinical Disease Characteristics at Baseline; Non-randomized and Continued to Receive Open-Label Treatment Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Mean (SD)	58.8 (20.14)
Median	60.0
Range	(3; 100)
IQ range	(45.0; 73.0)
PSSD symptom score (0-100)	
N	584
Mean (SD)	48.7 (24.01)
Median	48.0
Range	(0; 100)
IQ range	(30.0; 68.0)

[TSIDEM02C.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEM02C.SAS] 28MAR2016, 14:25

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TSIDEM03B: Summary of Medical History; Enrolled and Treated Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Analysis set: enrolled and treated subjects	871
Coronary artery disease (CAD)	19 (2.2%)
Myocardial infarction	10 (1.1%)
Angina pectoris	6 (0.7%)
Coronary artery bypass graft	5 (0.6%)
Percutaneous coronary intervention	4 (0.5%)
Peripheral vascular disease	6 (0.7%)
Transient ischemic attack (TIA)	3 (0.3%)
Stroke	1 (0.1%)
Diabetes mellitus	57 (6.5%)
Hyperlipidemia	112 (12.9%)
Hypertension	223 (25.6%)
Use of Cigarettes	
Current or former used	422 (48.5%)
Current user	289 (33.2%)
Never	449 (51.5%)
Smoking pack years[a]	
N	422
Mean (SD)	31.80 (116.340)
Median	13.71
Range	(0.0; 1809.9)
IQ range	(6.00; 25.92)
Family history of early coronary artery disease (<55 years of age)	72 (8.3%)
Asthma	42 (4.8%)
Depression	54 (6.2%)
Chronic liver disease (e.g., fatty liver disease, alcohol-induced, cirrhosis)	18 (2.1%)
Hospitalized within the past year (excluding pregnancy)	58 (6.7%)
Hospitalized within the past year for infection	4 (0.5%)
Skin squamous cell carcinoma (SCC)	9 (1.0%)
Skin basal cell carcinoma (BCC)	6 (0.7%)
Other malignancy	5 (0.6%)
Family history of cancer in a 1st degree relative (excluding skin squamous cell cancer carcinoma and skin basal cell cancer carcinoma)	148 (17.0%)

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TSIDEM03A: Summary of Medical History; Randomized Subjects (Study CNTO1959PSO3003)			
	Guselkumab	Ustekinumab	Total
Analysis set: randomized subjects	135	133	268
Coronary artery disease (CAD)	2 (1.5%)	4 (3.0%)	6 (2.2%)
Myocardial infarction	4 (3.0%)	1 (0.8%)	5 (1.9%)
Angina pectoris	0	1 (0.8%)	1 (0.4%)
Coronary artery bypass graft	0	1 (0.8%)	1 (0.4%)
Percutaneous coronary intervention	0	1 (0.8%)	1 (0.4%)
Peripheral vascular disease	0	0	0
Transient ischemic attack (TIA)	0	0	0
Stroke	0	0	0
Diabetes mellitus	4 (3.0%)	15 (11.3%)	19 (7.1%)
Hyperlipidemia	25 (18.5%)	23 (17.3%)	48 (17.9%)
Hypertension	39 (28.9%)	39 (29.3%)	78 (29.1%)
Use of Cigarettes			
Current or former used	63 (46.7%)	69 (51.9%)	132 (49.3%)
Current user	41 (30.4%)	47 (35.3%)	88 (32.8%)
Never	72 (53.3%)	64 (48.1%)	136 (50.7%)
Smoking pack years[a]			
N	63	69	132
Mean (SD)	30.36 (68.601)	56.56 (236.834)	44.06 (177.526)
Median	15.33	10.89	14.15
Range	(0.4; 538.5)	(0.0; 1809.9)	(0.0; 1809.9)
IQ range	(9.04; 30.94)	(5.50; 25.97)	(7.50; 29.43)
Family history of early coronary artery disease (<55 years of age)	14 (10.4%)	10 (7.5%)	24 (9.0%)
Asthma	9 (6.7%)	6 (4.5%)	15 (5.6%)
Depression	7 (5.2%)	18 (13.5%)	25 (9.3%)
Chronic liver disease (e.g., fatty liver disease, alcohol-induced, cirrhosis)	5 (3.7%)	5 (3.8%)	10 (3.7%)
Hospitalized within the past year (excluding pregnancy)	11 (8.1%)	7 (5.3%)	18 (6.7%)
Hospitalized within the past year for infection	0	0	0
Skin squamous cell carcinoma (SCC)	1 (0.7%)	1 (0.8%)	2 (0.7%)
Skin basal cell carcinoma (BCC)	1 (0.7%)	1 (0.8%)	2 (0.7%)
Other malignancy	0	0	0

Reference ID: 4084700

TSIDEM03A: Summary of Medical History; Randomized Subjects (Study CNTO1959PSO3003)			
	Guselkumab	Ustekinumab	Total
Family history of cancer in a 1st degree relative (excluding skin squamous cell cancer carcinoma and skin basal cell cancer carcinoma)	23 (17.0%)	25 (18.8%)	48 (17.9%)
Use of Alcohol			
Current or former used	92 (68.1%)	75 (56.4%)	167 (62.3%)
Current user	77 (57.0%)	65 (48.9%)	142 (53.0%)
Never used	43 (31.9%)	58 (43.6%)	101 (37.7%)

[a] Smoking pack years = number of years of smoking x number of pack of cigarettes per day

[TSIDEM03A.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEM03A.SAS] 08FEB2016, 11:38

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TSIDEM03C: Summary of Medical History; Non-randomized and Continued to Receive Open-Label Treatment Subjects (Study CNTO1959PSO3003)

	Ustekinumab
Analysis set: non-randomized and continued to receive open-label treatment subjects	585
Coronary artery disease (CAD)	13 (2.2%)
Myocardial infarction	5 (0.9%)
Angina pectoris	5 (0.9%)
Coronary artery bypass graft	4 (0.7%)
Percutaneous coronary intervention	3 (0.5%)
Peripheral vascular disease	6 (1.0%)
Transient ischemic attack (TIA)	3 (0.5%)
Stroke	1 (0.2%)
Diabetes mellitus	37 (6.3%)
Hyperlipidemia	63 (10.8%)
Hypertension	140 (23.9%)
Use of Cigarettes	
Current or former used	282 (48.2%)
Current user	195 (33.3%)
Never	303 (51.8%)
Smoking pack years[a]	
N	282
Mean (SD)	26.63 (73.993)
Median	13.41
Range	(0.0; 839.1)
IQ range	(5.43; 25.00)
Family history of early coronary artery disease (<55 years of age)	46 (7.9%)
Asthma	25 (4.3%)
Depression	29 (5.0%)
Chronic liver disease (e.g., fatty liver disease, alcohol-induced, cirrhosis)	8 (1.4%)
Hospitalized within the past year (excluding pregnancy)	37 (6.3%)
Hospitalized within the past year for infection	4 (0.7%)
Skin squamous cell carcinoma (SCC)	7 (1.2%)
Skin basal cell carcinoma (BCC)	4 (0.7%)
Other malignancy	5 (0.9%)
Family history of cancer in a 1st degree relative (excluding skin squamous cell cancer carcinoma and skin basal cell cancer carcinoma)	96 (16.4%)

Reference ID: 4084700

TSIDEM03C: Summary of Medical History; Non-randomized and Continued to Receive Open-Label Treatment Subjects (Study CNTO1959PSO3003)	
	Ustekinumab
Use of Alcohol	
Current or former used	324 (55.4%)
Current user	285 (48.7%)
Never used	260 (44.4%)

[a] Smoking pack years = number of years of smoking x number of pack of cigarettes per day

[TSIDEM03C.RTF] [CNTO1959\PSO3003\DBR_WEEK_040\RE_WEEK_040_CSR\PROD\TSIDEM03C.SAS] 08FEB2016, 11:38

(Clinical Study Report, pages 347-348 of 458)

7.4.6. CEC-Adjudicated Cardiovascular Events

Tables 10 through 13 summarize the CEC-adjudicated CV events.

Table 10. Study 3003: CEC-Adjudicated Cardiovascular Events, Randomized and Treated Subjects (Weeks 16-40)

	Guselkumab	Ustekinumab
# of subjects treated	135	133
Total subject-years of follow-up	62	59
MACE		
# of Events (%)	2 (1.48)	1 (0.75)
100 Subject-years	3.23	1.69
CV death		
# of Events (%)	0	0
100 Subject-years	0	0
Nonfatal MI		
# of Events (%)	2 (1.48)	1 (0.75)
100 Subject-years	3.23	1.69
Nonfatal Stroke		
# of Events (%)	0	0
100 Subject-years	0	0
All-Cause Mortality		
# of Events (%)	0	0
100 Subject-years	0	0
Non-CV death		
# of Events (%)	0	0
100 Subject-years	0	0
Other CV Events		
# of Events (%)	2 (1.48)	0
100 Subject-years	3.23	0
Hospitalization for Unstable Angina		
# of Events (%)	1 (0.74)	0
100 Subject-years	1.61	0
Arrhythmia Requiring Intervention		
# of Events (%)	1 (0.74)	0
100 Subject-years	1.61	0

CV: cardiovascular; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction
Analysis by Ququan Liu, MD, MS (Division of Biometrics 1)

Table 11. Study 3003: CEC-Adjudicated CV Events, Non-Randomized and Continued to Receive Open-Label Treatment Subjects (Weeks 16 – 40)

	Ustekinumab
# of subjects treated	585
Total subject-years of follow-up	270
MACE	
# of Events (%)	2 (0.34)
100 Subject-years	0.74
CV death	
# of Events (%)	0
100 Subject-years	0
Nonfatal MI	
# of Events (%)	1 (0.17)
100 Subject-years	0.37
Nonfatal Stroke	
# of Events (%)	1 (0.17)
100 Subject-years	0.37
All-Cause Mortality	
# of Events (%)	1 (0.17)
100 Subject-years	0.37
Non-CV death	
# of Events (%)	1 (0.17)
100 Subject-years	0.37
Other CV Events	
# of Events (%)	1 (0.17)
100 Subject-years	0.37
Arrhythmia Requiring Intervention	
# of Events (%)	1 (0.17)
100 Subject-years	0.37

CV: cardiovascular; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction
Analysis by Ruquan Liu, MD, MS (Division of Biometrics 1)

Table 12. Study 3003: CEC-Adjudicated CV Events (Through Week 16)

	Ustekinumab
# of subjects treated	871
Total subject-years of follow-up	270
MACE	
# of Events (%)	0
100 Subject-years	0
CV death	
# of Events (%)	0
100 Subject-years	0
Nonfatal MI	
# of Events (%)	0
100 Subject-years	0
Nonfatal Stroke	
# of Events (%)	0
100 Subject-years	0
All-Cause Mortality	
# of Events (%)	0
100 Subject-years	0
Other CV Events	
# of Events (%)	2 (0.23)
100 Subject-years	0.74
Arrhythmia Requiring Intervention	
# of Events (%)	2 (0.23)
100 Subject-years	0.74

CV: cardiovascular; MACE: major adverse cardiovascular events, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; MI: myocardial infarction
Analysis by Ruquan Liu, MD, MS (Division of Biometrics 1)

Table 13. Study 3003: CEC-Adjudicated Treatment Emergent Cardiovascular Events

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category	CEC Detailed Event Type	Serious (Y/N)	Reviewer Category and Comments
1	Ustekinumab	CNTO1959PSO3003-US90232-30490 57 yo white male (US)	Ustekinumab	114	(b) (6)	121	Acute myocardial infarction (AMI) (NSTEMI)-	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (history of CAD, unstable angina, hyperlipidemia, tobacco and marijuana use, and cocaine use/abuse. Subject reported daily cocaine use x 3 days. Had a positive urine screen in the Emergency Room)
2		CNTO1959PSO3003-PL00230-30266 48 yo white female (Poland)	Ustekinumab	113	(b) (6)	144	Retinal artery embolism (CENTRAL RETINAL ARTERY EMBOLISM OF THE RIGHT EYE)	Nonfatal stroke	Ischemic Stroke	Y	Ischemic Stroke (history of HTN and a positive family h/o premature CAD)
3		CNTO1959PSO3003-PL00227-30398 40 yo white female (Poland)	Ustekinumab	111	(b) (6)	133	Arrhythmia (CARDIAC ARRHYTHMIA)	Arrhythmia Requiring Intervention	Other Supra-ventricular Tachycardia	N	Supraventricular Tachycardia noted on 20MAY2015 Holter, but ER visit for symptomatic event for which patient was treated in the Emergency Room with intravenous fluids and given a beta blocker was on 3MARCH 2015.

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category	CEC Detailed Event Type	Serious (Y/N)	Reviewer Category and Comments
											(no major cardiac risk factors)
4		CNTO1959PSO3003-RU00371-30982 58 yo White male (Russia)	Ustekinumab	1	(b) (6)	1	Atrial Fibrillation (ATRIAL FIBRIL-LATION)	Arrhythmia Requiring Intervention	Atrial Fibrillation	N	No Event. This event occurred during screening prior to first dose of study drug. The CEC packet does not indicate that the subject was treated or that the underlying condition worsened during the course of the trial. On 28SEPT2015, the subject underwent a Cardiology Consultation. The consult reported that subject had shortness of breath at rest, palpitations, weakness, and malaise. Blood pressure was 160/80, with heart rate 85. The cardiologist's diagnoses were 1) Permanent atrial fibrillation; 2) hypertension; 3) aortic atherosclerosis; 4) Type II diabetes mellitus

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category	CEC Detailed Event Type	Serious (Y/N)	Reviewer Category and Comments
											(history of CAD, HTN, DM)
5	Ustekinumab (Randomized)	CNTO1959PSO3003-US01503-30096 66 yo Native Hawaiian or Other Pacific Islander (USA)	Ustekinumab	113	(b) (6)	128	AMI (STEMI)	Nonfatal MI	Type 1: Spontaneous	Y	AMI (STEMI) (history of CAD, HTN, HLP, tobacco use, and alcohol use)
6	Ustekinumab to Guselkumab 100 mg (Randomized)	CNTO1959PSO3003-US92304-30883 52 yo white male (US)	Guselkumab	113	(b) (6)	122	MI (INFERIOR WALL MI)	Nonfatal MI	Type 1: Spontaneous	Y	AMI (Inferior STEMI) (History of heavy tobacco use and prior history of alcoholism)
7		CNTO1959PSO3003-PL00235-30107 69 yo White female (Poland)	Guselkumab	169	(b) (6)	173	MI (MYO-CARDIAL INFARCT)	Nonfatal MI	Type 1: Spontaneous	Y	Nonfatal MI (history of HTN, HLP, obesity, CAD, and alcohol)
8			Guselkumab	169	(b) (6)	208	Angina unstable (UNSTABLE ANGINA PECTORIS)	Hospitaliza-tion for Unstable Angina		Y	Hospitalization for Unstable Angina
9		CNTO1959PSO3003-PL00233-30067 71 yo white male (Poland)	Guselkumab	197	(b) (6)	225	Sinus bradycardia (SINUS BRADY-CARDIA)	Arrhythmia Requiring Intervention	Bradycardia	N	Arrhythmia Requiring Intervention. Sinus bradycardia at 46 beats per minute due to high dose nebivolol for treatment of hypertension. Dose was reduced. Bradycardia

#	Treatment Group	Subject ID	Last Active Study Agent Received Prior to the Event	Study Day of Last Active Study Agent Prior to the Event	Date of Event	Study Day of Event	MedDRA Preferred Term (Verbatim Term)	CEC Event Category	CEC Detailed Event Type	Serious (Y/N)	Reviewer Category and Comments
											resolved at next visit.
10		CNTO1959PSO3003-DE00492-30412 51 yo white male (DEU)	Ustekinumab	29	(b) (6)	73	Atrial fibrillation (ATRIAL FIBRIL-LATION)	Arrhythmia Requiring Intervention	Atrial Fibrillation	Y	Arrhythmia Requiring Intervention (Atrial Fibrillation) (history of HTN)

AMI: acute myocardial infarction; CAD: coronary artery disease; DM: diabetes mellitus; HLP: hyperlipidemia; HTN: hypertension; MI: myocardial infarction; NSTEMI: non-ST-segment elevation MI; STEMI: ST-elevation MI.
Note: There was a non-CV death due to metastatic pancreatic carcinoma in Subject PSO3003-PL00165-30288 on (b) (6) (Day 292), which occurred approximately 2 weeks after Week 40. Since the subject was diagnosed with cancer prior to Week 40, we included this non-CV death in our analysis. This subject was receiving non-randomized open-label ustekinumab.
Adapted from Sponsor. Response to Information Request dated March 24, 2017.

8. Cardiovascular Events Reported in the 120-Day Safety Update Report

On March 16, 2017, the applicant submitted the 120-Day Safety Update Report for BLA 761061 dated March 1, 2017. The following events have been identified after database lock for which we do not currently have any data:

Study 3001

- 1 non-CV death (Subject CNTO1959PSO3001-10990) due to suicide (Day 492) (open-label guselkumab)
- 1 non-CV death due to brain neoplasm (Subject HU36004-10594) (Day 560) (open-label guselkumab)
- 1 pulmonary embolism (Subject DE00481-10253) (guselkumab)

Study 3002

- 1 non-CV death due to diabetic coma (US02021-21191)
- 1 acute MI (STEMI) (Subject PL00230-20278) (Day 487) (Retreatment)
- 1 acute MI (NSTEMI) (Subject PL00244-20889) (Day 389) (Withdrawal)
- 1 MI with occlusion of the left anterior descending artery (Subject CA90097-20346) (Day 515) (guselkumab)
- 1 bilateral pulmonary embolus (Subject CA00185-20393) (Day 539)(Retreatment)
- 1 branch retinal vein occlusion left eye (Subject DE00500-20970) (Day 347) (Withdrawal)
- 1 hypertension requiring hospitalization (Subject PL00165-20075) (Day 455) (placebo → guselkumab)
- 1 atrial fibrillation (Subject PL00234-20133) (Day 337) (guselkumab)
- 1 unstable angina (Subject US92404-20995) (Day 437) (adalimumab → guselkumab)
- 1 bradycardia due to nebivolol (Subject 21096) (Day 357) (adalimumab → guselkumab)

Study 3003

- 1 non-CV death (Subject PL0016530102) due to squamous cell carcinoma of the neck

9. Summary of Key Findings

See the Executive Summary.

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/s/

KAREN A HICKS
04/14/2017

NORMAN L STOCKBRIDGE
04/17/2017

Office of Clinical Pharmacology Review

BLA Number	761061
Link to EDR	\\CDSESUB1\EVSPROD\BLA761061\761061.enx
Submission Date	November 16, 2016
Submission Type (Priority or Standard)	Original BLA, New Molecular Entity (*Priority review)*
Brand Name	TRADENAME
Generic Name	Guselkumab
Dosage Form and Strength	100 mg/mL solution in single-use prefilled syringe
Route of Administration	Subcutaneous injection
Proposed Indication	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Applicant	Janssen Biotech, Inc.
Associated IND	105,004
OCP Review Team	Anand Balakrishnan, Ph.D. Simbarashe Peter Zvada, Ph.D. Jeffry Florian, Ph.D. Yow-Ming Wang, Ph.D.
OCP Final Signatory	Hae-Young Ahn, Ph.D., Deputy Director, Division of Clinical Pharmacology 3

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized.

Refer to the Multi-disciplinary Review and Evaluation for additional details. The proposed dosing regimen of 100 mg of guselkumab administered by subcutaneous injection at Weeks 0, 4, and every 8 weeks thereafter has demonstrated clinical efficacy with a tolerable safety profile; therefore the proposed dosing regimen is acceptable.

From a Clinical Pharmacology standpoint, the BLA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

Reference ID: 4084675

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/s/

ANAND BALAKRISHNAN
04/14/2017

SIMBARASHE P ZVADA
04/14/2017

JEFFRY FLORIAN
04/14/2017

YOW-MING C WANG
04/14/2017

HAE YOUNG AHN
04/14/2017

Memorandum

To: BLA 761061
From: Renqin Duan, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

SDN: 1
Submission date: 11-16-2016
Submission type: Original BLA
Drug: Guselkumab injection
Indication: Moderate-to-severe plaque psoriasis
Route: Subcutaneous injection
Applicant: Janssen Biotech, Inc.

The applicant submitted an original 351a BLA application for Guselkumab Injection indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) directed against the p19 subunit of interleukin 23 (IL-23). The nonclinical pharmacology/toxicology review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for details.

Guselkumab is approvable for the treatment of moderate-to-severe plaque psoriasis from a Pharmacology/Toxicology perspective. There are no recommended nonclinical PMCs/PMRs for this BLA.

Reference ID: 4082681

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/s/

Renqin DUAN
04/11/2017

BARBARA A HILL
04/11/2017