27 March 2025
EMA/CHMP/444643/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tremfya

International non-proprietary name: guselkumab

Procedure No. EMEA/H/C/004271/II/0044

Note

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

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List of abbreviations

Abbreviation	Definition
6-MP	6-mercaptopurine
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	abdominal pain
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AZA	Azathioprine
BIO-Failure	biologic therapy failure or intolerance
C_{ave}	average concentration
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
CL/F	apparent clearance
C_{max}	maximum observed serum concentration
CMV	Cytomegalovirus
CO	Clinical Overview
COVID-19	Coronavirus Disease 2019
CON-Failure	conventional therapy failure or intolerance
CRP	C-reactive protein
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	trough concentration
DBL	database lock
DILI	drug-induced liver injury
ECLIA	electrochemiluminescence immunoassay
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
F	absolute bioavailability
FDA	Food and Drug Administration (US)
FOIA	Freedom of Information Act
FVP	final vialed product (for IV injection)
GALAXI	CNTO1959CRD3001 (protocol)
GRAVITI	CNTO1959CRD3004 (protocol)
GCP	Good Clinical Practice
GI	Gastrointestinal
GUS	Guselkumab
HRQOL	health-related quality of life

IA	interim analysis
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	intercurrent events
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG1λ	immunoglobulin G1 lambda
IL	Interleukin
IV	intravenous(ly)
JAK	Janus kinase
k_a	first-order absorption rate constant
LFT	liver function test
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAb	neutralizing antibody
NI	non-inferiority
NMSC	nonmelanoma skin cancer
NRS	numeric rating scale
PCS	physical component score
PD	pharmacodynamic(s)
PFP	prefilled pen
PFS	prefilled syringe
PFS-S	prefilled syringe assembled with the One-Press™ Patient-controlled Injector
PFS-U	prefilled syringe assembled with the UltraSafe Plus™ Needle Guard
PFS-Y	prefilled syringe assembled with the YpsoMate™ Autoinjector
PK	pharmacokinetic(s)
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS-29	29-question Patient-Reported Outcomes Measurement Information System (instrument)
PROMIS-Fatigue SF-7a	PROMIS-Fatigue Short Form 7a
PsA	psoriatic arthritis
PT	preferred term
Q	intercompartmental clearance
q4w	every 4 weeks
q8w	every 8 weeks
RLPH	Real Life Patient Handling
RMP	Risk Management Plan
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBAAM	Summary of Biopharmaceutics and Associated Analytical Methods
SC	subcutaneous(ly)

SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SmPC	Summary of Product Characteristics
SOC	System Organ Class
$T_{1/2}$	terminal elimination half-life
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States (of America)
V	volume(s) of distribution
Vc	central volume of distribution
V_c	central volume of distribution
V_{ss}/F	apparent volume of distribution at steady state
V_p	peripheral volume of distribution
V_{ss}	volume of distribution at steady state
VTE	venous thromboembolism
WPAI-CD	Work Productivity and Activity Impairment Questionnaire in Crohn's Disease

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 29 April 2024 an application for a variation.

The following variation was requested:

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

Extension of indication for TREMFYA to include treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment, based on results from GALAXI Phase 2/3 program and the GRAVITI Phase 3 study. GALAXI is a Phase 2/3, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter protocol to evaluate the efficacy and safety of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional or biologic therapy. GRAVITI is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in participants with moderately to severely active CD.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0065/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0065/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the assessment of the

procedure, the MAH withdrew their request for one additional year of market protection.

Scientific advice

The MAH received several Scientific Advices from the CHMP. These Advices pertained to quality and clinical aspects of the dossier. See Section 2.1.3 for more details.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Beata Maria Jakline Ullrich

Timetable	Actual dates
Submission date	29 April 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	23 August 2024
PRAC Rapporteur Assessment Report	23 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	29 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 September 2024
Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	20 November 2024
PRAC Rapporteur Assessment Report	20 November 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	28 November 2024
CHMP members comments	03 December 2024
Updated CHMP Rapporteur Assessment Report	10 December 2024
Request for supplementary information	12 December 2024
CHMP Rapporteur Assessment Report	25 February 2025
PRAC Rapporteur Assessment Report	27 February 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	13 March 2025
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	20 March 2025

Timetable	Actual dates
CHMP opinion	27 March 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Crohn's disease (CD) is a chronic, progressive, and potentially life-threatening disorder that may affect any part of the gastro-intestinal (GI) tract. Symptoms may include diarrhea, abdominal pain, weight loss/anorexia, and fatigue. Inflammation can cause mucosal ulcerations to form and can also penetrate the lining of the GI tract, causing intra-abdominal fistulas, in addition to causing painful perianal disease. Crohn's disease may also be stricturing, such that patients may require repeated surgeries.

The pathophysiology of CD is complex and thought to be multifactorial (D'Haens 2014[1]).

State the claimed therapeutic indication

The indication for guselkumab in the treatment of Crohn's disease initially applied is as follows:

Tremfya is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.

Epidemiology

CD incidence is highest in North America and Europe, with estimates of 15 per 100,000 person-years in Europe, respectively. The prevalence in Europe is 322 per 100,000 persons. The incidence of CD worldwide has increased over the last three decades, particularly in newly industrialised countries.

Aetiology and pathogenesis

Chronic inflammation from T-cell activation leading to tissue injury is implicated in the pathogenesis of CD.

After activation by antigen presentation, unrestrained responses of type 1 T helper (Th1) cells predominate in CD as a consequence of defective regulation. Th1 cytokines such as interleukin (IL)-12 and TNF-α stimulate the inflammatory response. Inflammatory cells recruited by these cytokines release nonspecific inflammatory substances, including arachidonic acid metabolites, proteases, platelet activating factor, and free radicals, which result in direct injury to the intestine.

[1] D'Haens GR (2014), Sartor RB, Silverberg MS, Petersson J, Rutgeerts P. Future directions in inflammatory bowel disease management. J Crohn's Colitis. 2014;8(8):726-734.

The exact cause of CD remains unknown. Genetic, microbial, immunologic, environmental, dietary, vascular, and psychosocial factors have been implicated, as have smoking and the use of oral contraceptives and nonsteroidal anti-inflammatory agents (NSAIDs). Patients may inherit susceptibility for an aberrant immunologic response to one or more of these provoking factors. Interaction between the predisposing genetic factors, environmental factors, host factors, and triggering event is likely necessary for the disease to develop.

Clinical presentation, diagnosis and stage/prognosis

The disease affects the GI tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (approximately 40%), followed by a disease in the small bowel only (approximately 30%), in the colon only (approximately 25%), and other locations (approximately 5%). Some patients may have a continuously clinically active disease. A diagnosis is usually based on composite clinical and pathological features and the exclusion of alternative disease states.

CD has been classified by disease phenotype into primarily inflammatory disease, stricturing disease or penetrating disease modified by the presence of upper gastrointestinal or perianal disease (in up to 20%) (Montreal classification 2005).

Over the course of the disease, phenotype commonly changes from predominantly inflammatory disease to stricturing and/or penetrating disease.

The major signs and symptoms are diarrhoea, abdominal pain and weight loss, partly determined by the anatomical location and the severity of the disease. There may be no direct correlation between an individual's symptoms and endoscopic and radiological findings.

Management

The primary aim of pharmacotherapy is to dampen the inflammatory response, thereby relieving symptoms and promoting mucosal healing. The specific goals of CD treatment include control of symptoms, prevention of relapses and complications, restoration and maintenance of quality of life, and absence of disability (Turner 2021[2]).

The treatment of CD has historically relied on corticosteroids and immunosuppressive medications such as thiopurines or methotrexate (MTX). Corticosteroids are associated with well-known undesired side effects and therefore are not suitable for long-term treatment.

Biologic agents currently approved for the treatment of moderately to severely active CD include: TNF antagonist therapies, an α4β7-integrin inhibitor, an IL-12/23 inhibitor, and an IL-23p19 inhibitor. A Janus kinase (JAK) inhibitor is also approved. Despite the availability of these approved therapies, not all patients respond to induction therapy and many patients who initially respond to the approved therapies may lose response over time. It is estimated that more than half of patients with CD fail to achieve corticosteroid-free clinical remission after 1 year, with even fewer achieving endoscopic response or remission (Singh 2021[3]; Vuyyuru 2024[4]). The importance of achieving endoscopic outcomes in CD has been increasingly recognized in recent consensus statements and guidelines to

[2] Turner D (2021), Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.
[3] Singh S (2021), Proctor D, Scott FI, Falck-Ytter Y, Feuerstein JD. AGA Technical Review on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160(7):2512-2556.e9.

[4] Vuyyuru SK (2024), Nguyen TM, Murad MH, et al. Comparative Efficacy of Advanced Therapies for Achieving Endoscopic Outcomes in Crohn's Disease: A Systematic Review and Network Meta-Analysis. Clin Gastroenterol Hepatol. Published online January 6, 2024.

improve long-term outcomes (Christensen 2016[5]; Turner 2021[6]), adding to the unmet need in the treatment of CD. Furthermore, there are associated safety risks with the approved medicines, including warnings related to serious infections, mortality, malignancy, major adverse cardiovascular events, or thrombosis. Hence, there is an unmet medical need for additional efficacious therapeutic options in CD with a favourable safety profile for patients with an inadequate response to or intolerance to conventional or biologic therapies.

2.1.2. About the product

Guselkumab (Tremfya) is an Interleukin Inhibitor (ATC code: L04AC16). Guselkumab is a fully human IgG1λ mAb that binds to the p19 protein sub-unit of IL-23 with high specificity and affinity.

IL-23 is a naturally occurring dominant regulatory cytokine that affects the expansion and survival of human CD4 IL-17 producing Th17 cells and CD8 IL-17 producing Tc17 cells that are known to drive inflammatory disease (Ciric 2009[7]; Sewell 2022[8]; Verstockt 2023[9]). The contribution of the IL-23/IL-17 pathway to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases has become established (Ouyang 2008[10]; Tato 2006[11]). IBD is associated with genetic polymorphisms in IL-23/IL-23R components (Duerr 2006[12]; Kim 2011[13]; Peng 2017[14]; Xu 2015[15]).

By binding to the p19 protein subunit of IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-mediated intracellular signaling, activation, and cytokine production.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The guselkumab adult clinical development programme for the treatment of moderately to severely active CD was designed in consideration of the EMA Guideline on the development of new medicinal products for the treatment of CD (CHMP/EWP/2284/99 Rev.2).

In addition, Scientific advices were given by the CHMP and pertained to the followings:

- Guselkumab CD Phase 2/3 overall clinical program (GALAXI) and quality development for new IV formulation

[5] Christensen B (2016), Rubin DT. Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice. Curr Gastroenterol Rep. 2016;18(1):5.
[6] Turner D (2021), Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.
[7] Ciric B (2009), El-behi M, Cabrera R, Zhang GX, Rostami A. IL-23 drives pathogenic IL-17-producing CD8+ T cells. J Immunol. 2009;182(9):5296-5305.
[8] Sewell GW (2022), Kaser A. Interleukin-23 in the Pathogenesis of Inflammatory Bowel Disease and Implications for Therapeutic Intervention. J Crohns Colitis. 2022;16(Supplement_2):ii3-ii19.
[9] Verstockt B (2023), Salas A, Sands BE, et al. IL-12 and IL-23 pathway inhibition in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2023;20(7):433-446.
[10] Ouyang W (2008), Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008;28(4):454-467.
[11] Tato CM (2006), O'Shea JJ. Immunology: what does it mean to be just 17?. Nature. 2006;441(7090):166-168.
[12] Duerr RH (2006), Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314(5804):1461-1463.
[13] Kim SW (2011), Kim ES, Moon CM, et al. Genetic polymorphisms of IL-23R and IL-17A and novel insights into their associations with inflammatory bowel disease. Gut. 2011;60(11):1527-1536.
[14] Peng LL (2017), Wang Y, Zhu FL, Xu WD, Ji XL, Ni J. IL-23R mutation is associated with ulcerative colitis: A systemic review and meta-analysis. Oncotarget. 2017;8(3):4849-4863.
[15] Xu WD (2015), Xie QB, Zhao Y, Liu Y. Association of Interleukin-23 receptor gene polymorphisms with susceptibility to Crohn's disease: A meta-analysis. Sci Rep. 2015;5:18584.

- Guselkumab CD GALAXI Phase 3 studies - Week 48 major secondary endpoints and statistical approach
- Guselkumab CD SC induction Phase 3 study (GRAVITI)
- EMA Qualification Advice - PROMIS-29 and PROMIS-Fatigue SF-7A

2.2. Non-clinical aspects

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

In order to support the posology recommended in CD, the applicant has updated the safety margins at the NOAEL dose.

2.2.1. Toxicology

Repeat dose toxicity

Updated safety margins at the NOAEL dose (50 mg/kg SC once weekly) in monkeys are as follows for the proposed dosing regimen:

- 400 mg SC Induction followed by 100 mg SC Maintenance: approximately 31 or 22 times the exposure (based on Cmax or AUC, respectively) in humans administered the 400 mg SC induction dose, and 123 or 231 times the exposure (based on Cmax or AUC, respectively) at the 100 mg SC maintenance dose.
- 400 mg SC Induction followed by 200 mg SC Maintenance: approximately 31 or 22 times the human exposure (based on Cmax or AUC, respectively) during induction at a dose of 400 mg SC, and 62 or 44 times the human exposure (based on Cmax or AUC, respectively) at the 200 mg SC maintenance dose.

Reproduction toxicity

There were no effects on fertility parameters observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 100 mg/kg twice weekly.

Updated safety margins for female guinea pigs are as follows for the proposed dosing regimen:

- 400 mg SC Induction followed by 100 mg SC Maintenance: approximately 16 or 10 times the exposure (based on Cmax or AUC, respectively) in humans administered the 400 mg SC induction dose, and 63 or 109 times the exposure (based on Cmax or AUC, respectively) the 100 mg SC maintenance dose.
- 400 mg SC Induction followed by 200 mg SC Maintenance: approximately 16 or 10 times the exposure (based on Cmax or AUC, respectively) in humans administered the 400 mg SC induction dose, and 32 or 21 times the exposure (based on Cmax or AUC, respectively) the 200 mg SC maintenance dose.

There were no effects on fertility parameters observed after male guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly.

- 400 mg SC Induction followed by 100 mg SC Maintenance: approximately 32 or 22 times the exposure (based on Cmax or AUC, respectively) in humans administered the 400 mg SC induction dose, and 125 or 233 times the exposure (based on Cmax or AUC, respectively) at the 100 mg SC maintenance dose.
- 400 mg SC Induction followed by 200 mg SC Maintenance: approximately 32 or 22 times the exposure (based on Cmax or AUC, respectively) in humans administered the 400 mg SC induction dose, and 63 or 45 times the exposure (based on Cmax or AUC, respectively) at the 200 mg SC maintenance dose.

There were no effects on reproduction or development in an ePPND study in which pregnant cynomolgus monkeys were administered guselkumab SC at doses up to 50 mg/kg/week from GD20 through natural delivery and infants evaluated for 6 months after birth. There was a slightly higher incidence of pregnancy losses in the guselkumab treatment groups (10 or 50 mg/kg/week SC) relative to controls but without clear dose-response relationship.

- 400 mg SC Induction followed by 200 mg SC Maintenance: no adverse developmental effects were observed in infants born to pregnant monkeys after SC administration of guselkumab during organogenesis through parturition at exposures up to 23 or 16 times (based on Cmax or AUC, respectively) the exposure in humans administered the 400 mg SC induction dose, and 46 or 32 times the exposure (based on Cmax or AUC, respectively) following the 200 mg maintenance dose. Neonatal deaths were observed at both doses tested (10 mg/kg and 50 mg/kg) with associated exposure (AUC) 4 to 18 times the exposure in humans administered the 400 mg SC induction dose and 7 to 32 times the exposure (AUC) to the 200 mg SC maintenance dose.

2.2.2. Ecotoxicity/environmental risk assessment

Guselkumab is a monoclonal antibody that does not incorporate any non-natural amino acids. Hence, it is considered a natural protein expected to be readily degraded. Therefore, guselkumab is not expected to pose a significant risk to the environment in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.2.3. Discussion and conclusion on non-clinical aspects

No new non-clinical data have been submitted.

No new toxicology study was carried out to support the CD indication. However, the NOAEL values were recalculated for general repeat dose toxicity and reproductive toxicity. The SmPC Section 5.3 is updated accordingly to indicate that a weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 22 times the maximum clinical exposures following a dose of 400 mg given subcutaneously.

Guselkumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Summary of Clinical Efficacy Studies of Guselkumab in CD

Study ID/Phase	Number of Study Centers/Countries or Territories	Study Start/ Status	Study Design	Dose Regimens	Patient Population Inclusion Criteria	Objective(s)
CNTO1959CRD3001 GALAXI 1/ Phase 2	128/32	10 May 2018/ Ongoing	Randomized, double-blind, placebo- and active-controlled (ustekinumab reference arm), treat-through, dose-ranging	1:1:1:1:1 ratio to receive the 1 of the following: • Guselkumab Regimen 1: 1200 mg IV q4w ×3 → 200 mg SC q4w • Guselkumab Regimen 2: 600 mg IV q4w ×3 → 200 mg SC q4w • Guselkumab Regimen 3: 200 mg IV q4w ×3 → 100 mg SC q8w • Ustekinumab: ~6 mg/kg IV → 90 mg SC q8w • Placebo → Placebo or Ustekinumab Crossover at Week 12	≥18 years of age with moderately to severely active CD (≥3 months' duration); CON or BIO-Failure	• To evaluate the clinical efficacy of guselkumab in participants with CD • To evaluate the safety of guselkumab
GALAXI 2 Phase 3	186/36	08 January 2020/ Ongoing	Randomized, double-blind, placebo- and active-controlled (ustekinumab), treat-through, confirmatory	2:2:2:1 ratio to receive the 1 of the following: • Guselkumab Regimen 1 (200 mg IV q4w ×3 → 200 mg SC q4w) • Guselkumab Regimen 2 (200 mg IV q4w ×3 → 100 mg SC q8w) • Active Control – Ustekinumab (~6 mg/kg IV → 90 mg SC q8w) • Placebo → Placebo or Ustekinumab Crossover at Week 12	≥18 years of age with moderately to severely active CD (≥3 months' duration); CON or BIO-Failure	• To evaluate the clinical and endoscopic efficacy of guselkumab in participants with CD • To evaluate the safety of guselkumab
GALAXI 3 Phase 3	198/39	22 January 2020/ Ongoing	Randomized, double-blind, placebo- and active-controlled (ustekinumab), treat-through, confirmatory	• Same as GALAXI 2	≥18 years of age with moderately to severely active CD (≥3 months' duration); CON or BIO-Failure	• Same as GALAXI 2

Table 1: Summary of Clinical Efficacy Studies of Guselkumab in CD

Study ID/Phase	Number of Study Centers/Countries or Territories	Study Start/ Status	Study Design	Dose Regimens	Patient Population Inclusion Criteria	Objective(s)
CNTO1959CRD3004 (GRAVITI)/ Phase 3	143/23	22 February 2022/Ongoing	Randomized, double-blind, placebo-controlled, treat-through	1:1:1 ratio to receive the 1 of the following: • Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 200 mg SC q4w through Week 24 • Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 100 mg SC q8w through Week 24 • Placebo SC → placebo SC or→ guselkumab rescue at Week 16	≥18 years of age with moderately to severely active CD (≥3 months' duration); CON or BIO-Failure	• To evaluate the clinical and endoscopic efficacy of guselkumab SC induction • To evaluate the safety of guselkumab SC

2.3.2. Pharmacokinetics

Biopharmaceutics and Bioanalytics

The same bioanalytical methods were used for the clinical studies in CD and UC, and the same Phase 1 studies were used to support the development of formulations and SC delivery devices for both indications.

Pharmacokinetics in CD patients

Study GALAXI 1 (CNTO1959CRD3001)

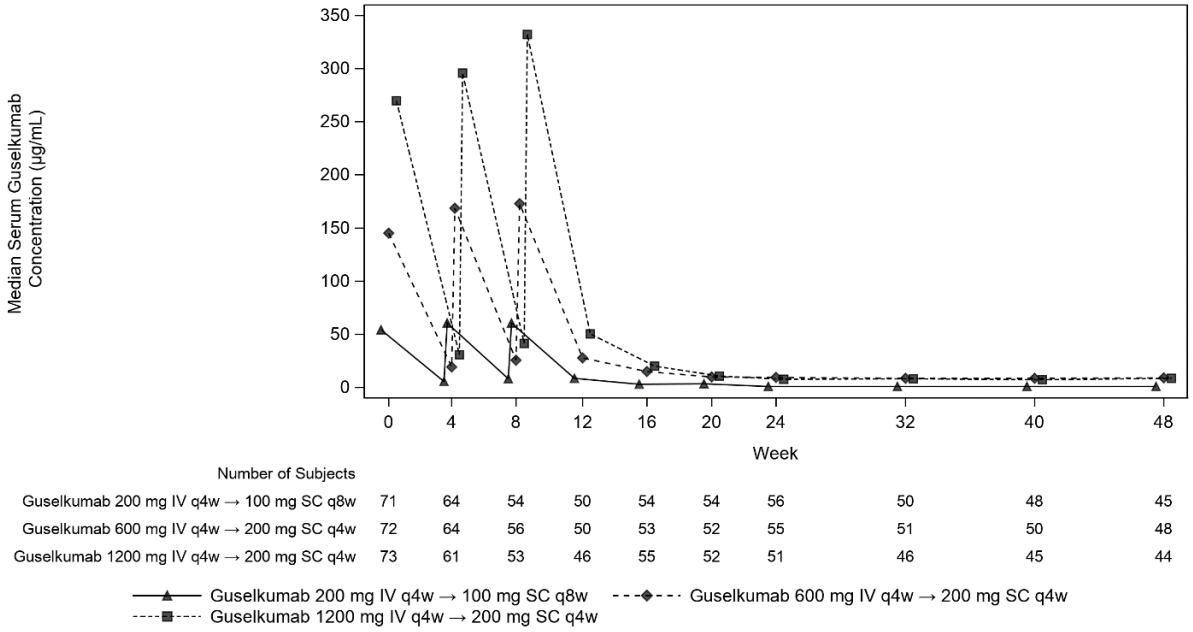
GALAXI 1 is a Phase 2, dose-ranging study with guselkumab dose regimens spanning a wide (6-fold) induction dose range to support the dose regimens selection for confirmatory evaluation in Phase 3 studies.

Study design is provided in the Clinical Efficacy Section 2.4.1.

Pharmacokinetic Results

Serum concentrations of guselkumab were measured from blood samples collected at scheduled timepoints through Week 48 (Figure 1).

Figure 1: Median Serum Guselkumab Concentrations (µg/mL) Through Week 48 (CNTO1959CRD3001 Phase 2 GALAXI 1; PK Analysis Set)



Phase 3 GALAXI Confirmatory Studies (GALAXI 2 and GALAXI 3)

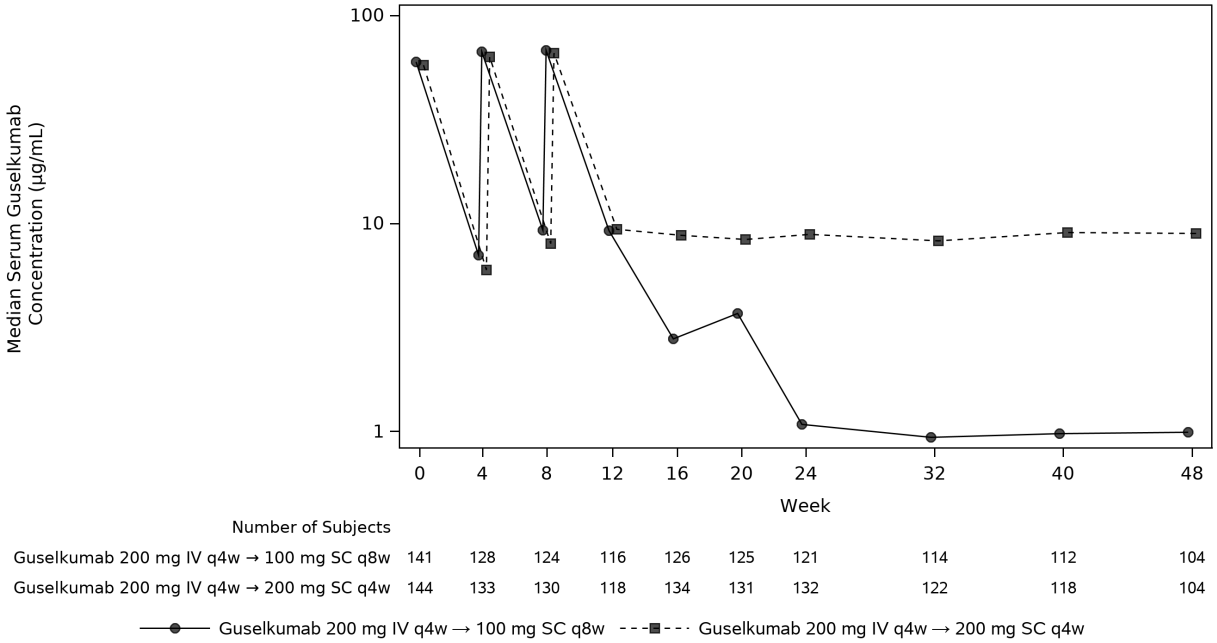
GALAXI 2 and 3 are 2 identical Phase 3, dose-confirming, randomized, double-blind, placebo- and active-controlled (ustekinumab), parallel-group, multicenter protocol studies to evaluate the efficacy and safety of guselkumab. Study design is provided in the Clinical Efficacy Section 2.4.2.1. The data presented in the following sections are for the primary guselkumab PK analysis set, which included participants with a screening SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease).

Study GALAXI 2

Serum Guselkumab Concentrations Through Week 48

At each post-dose sampling timepoint through Week 12, median serum guselkumab concentrations were similar between guselkumab treatment groups (Figure 2).

Figure 2: Median Serum Guselkumab Concentrations (µg/mL) Through Week 48; (CNTO1959CRD3001 Phase 3 GALAXI 2; Primary Guselkumab PK Analysis Set)



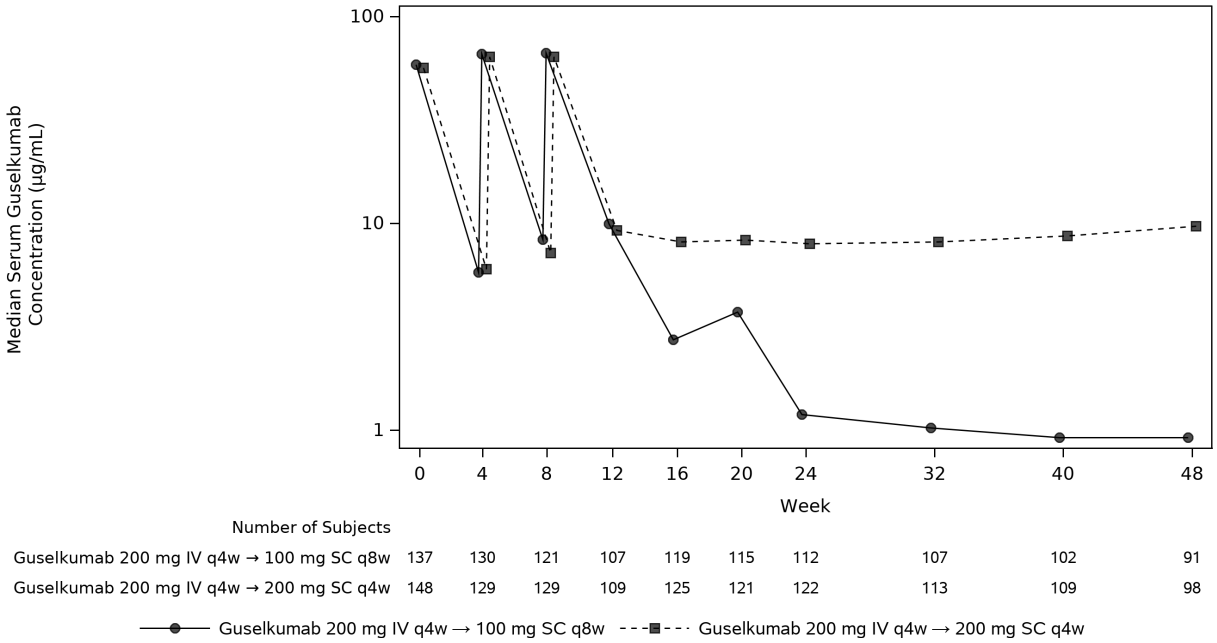
Abbreviations: IV=intravenous; PK=pharmacokinetic; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous.
Note: The first timepoint in the graph is 1 hour post dose.

Study GALAXI 3

Serum Guselkumab Concentrations Through Week 48

At each post-dose sampling timepoint through Week 12, the median serum guselkumab concentrations were similar between the guselkumab treatment groups (Figure 3).

Figure 3: Median Serum Guselkumab Concentrations (µg/mL) Through Week 48 (CNTO1959CRD3001 Phase 3 GALAXI 3; Primary Guselkumab PK Analysis Set)



Abbreviations: IV=intravenous; PK=pharmacokinetic; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous.
Note: The first timepoint in the graph is 1 hour post dose.

Phase 3 GRAVITI Study (CNTO1959CRD3004)

GRAVITI is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC treatment through 12 weeks of induction treatment and at least 12 weeks of maintenance treatment (24-week main study period).

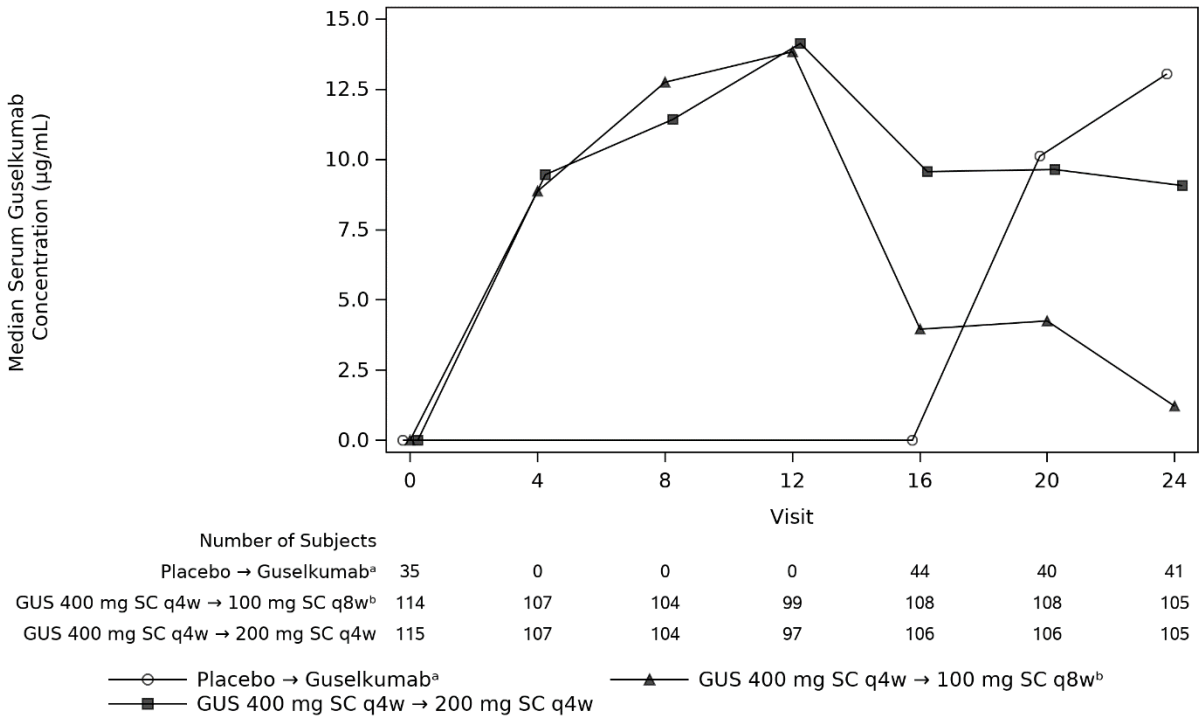
Study design is provided in the Clinical Efficacy Section 2.4.2.1.

Serum Guselkumab Concentrations Through Week 24

Prior to Week 12, participants in both the 200 mg SC q4w and 100 mg SC q8w groups received the same guselkumab dose regimen (400 mg SC q4w at Weeks 0, 4 and 8). After the last 400 mg SC induction dose of guselkumab at Week 8, participants randomized to the 400 mg SC q4w→200 mg SC q4w group began receiving maintenance guselkumab 200 mg SC q4w starting at Week 12, while those randomized to the 400 mg SC q4w→100 mg SC q8w group began receiving maintenance guselkumab 100 mg SC q8w starting at Week 16. Participants in the placebo group who met rescue criteria at Weeks 12 and 16 received guselkumab 400 mg SC at Weeks 16, 20, and 24.

Median serum guselkumab concentrations (µg/mL) through Week 24 are presented in Figure 4.

Figure 4: Median Serum Guselkumab Concentrations (µg/mL) Through Week 24 (CNTO1959CRD3004 Phase 3 GRAVITI; PK Analysis Set)



Number of Subjects							
Placebo → Guselkumab[a]	35	0	0	0	44	40	41
GUS 400 mg SC q4w → 100 mg SC q8w[b]	114	107	104	99	108	108	105
GUS 400 mg SC q4w → 200 mg SC q4w	115	107	104	97	106	106	105

Abbreviations: GUS=guselkumab; PK=pharmacokinetic; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous.Note: At dosing visits, samples were taken prior to study agent administration. Note: Guselkumab 400 mg SC administered at Weeks 0, 4, and 8. a Participants received placebo at Weeks 0, 4, 8, and 12. Participants received guselkumab 400 mg SC at Weeks 16, 20, and 24. b Participants did not receive guselkumab at Weeks 12 and 20.

Population Pharmacokinetic Analysis

Model Development

The population PK analysis of guselkumab in participants with moderately to severely active CD was performed using integrated data from GALAXI 1, GALAXI 2 and 3, and GRAVITI studies. The integrated PK data were based on the PK analysis sets from each study and consist of all randomized participants who received at least 1 dose of guselkumab, satisfied the SES-CD criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]), and had at least 1 valid post-baseline PK measurement.

The final integrated PK data comprised 10,632 serum guselkumab concentrations from 1,009 participants, with 197, 289, and 293 participants from GALAXI 1, 2, and 3, respectively (database lock at Week 48), as well as 230 participants from GRAVITI (database lock at Week 24), who were exposed to guselkumab from Week 0.

The population PK analysis was performed using nonlinear mixed effects modeling (NONMEM) software.

The participants in the final population PK dataset had a median age of 35 years (range: 18 to 83 years) and a median body weight of 67.3 kg (range: 28.2 to 158 kg). In this dataset, 39 (3.9%) participants were ≥65 years of age (and included 5 [0.5%] participants ≥75 years of age). Most participants were male (57.8%) and Caucasian (69.8%). There were 106 (10.5%) Chinese and 41 (4.1%) Japanese participants. Approximately half of the participants (51.0%) had previously failed or were intolerant to biologic therapy. The median disease duration was 5.27 years (range: 0.16 to 46.4 years), the median baseline CDAI score was 288 (range: 180 to 447), the median baseline CRP

was 6.40 mg/L (range: 0.1 to 252 mg/L), and the median baseline fecal calprotectin was 889 mg/kg (range: 15 to 36,000 mg/kg). Concomitant immunomodulators (ie, AZA, 6-MP, MTX) were used by 30.9% of participants at baseline and corticosteroids were used by 35.4% of participants at baseline. Overall, few participants had antibodies to guselkumab following treatment (42 out of 1009 participants [4.2%]).

The covariate assessment focused primarily on the effect of covariates on CL, except for body weight, which was also assessed on V.

Final Population Pharmacokinetic Model

The observed guselkumab serum concentration-time profiles in participants with CD were adequately described by a 2-compartment linear PK model with first-order absorption for SC administration and first-order elimination.

All parameters were estimated with good precision, with RSEs of less than or close to 20%. For a typical individual (body weight of 70 kg), guselkumab CL was estimated as 0.304 L/day and V_{ss} (V_c+V_p) as 6.12 L (Table 2). Based on the estimate of the absolute bioavailability (F1, i.e., F) of guselkumab following SC administration in a typical individual in the final model (53.5%), the estimated CL/F and V_{ss}/F were 0.568 L/day and 11.4 L, respectively. The model-derived $T_{1/2}$ in a typical individual was estimated as 16.8 days.

In the final population PK model, body weight, baseline serum albumin, baseline CRP, and prior biologic failure status were identified as statistically significant covariates on guselkumab CL. Body weight was identified as a statistically significant covariate on volume of distribution (V_c and V_p). In the final population PK model, higher body weight, lower serum albumin, higher CRP levels, and history of prior failure to biologics were all associated with higher CL. All other covariates tested, including antibodies to guselkumab, age (≥65 years vs <65 years), sex, race, Chinese ethnicity, Japanese ethnicity, immunomodulator use at baseline, corticosteroid use at baseline, hepatic function measurement, current smoking status, and past/current diabetes history were not associated with CL.

Table 2*:* Parameter estimates from the final population PK model for guselkumab in participants with moderately to severely active CD

Parameters	Estimate	RSE (%)[a]	95% CI	Magnitude of Change[b]
Clearance (CL; L/day)[c]	0.304	2.29	(0.29, 0.318)	-
Exponent for the effect of body weight on CL and Q	0.618	6.54	(0.539, 0.697)	-10.3% to +11.1%
Exponent for the effect of baseline serum albumin on CL	-1.20	7.52	(-1.38, -1.02)	+9.1% to -7.8%
Exponent for the effect of baseline C-reactive protein on CL	0.0281	20.2	(0.017, 0.0392)	-3% to +3%
Additive effect of prior biologic failure status on CL	0.118	14.5	(0.0845, 0.152)	+11.8%
Central volume of distribution (V_c; L)[d]	3.59	0.85	(3.53, 3.65)	-
Exponent for the effect of body weight on V_c and V_p	0.55	4.87	(0.497, 0.603)	-9.3% to +9.8%
Intercompartmental clearance (Q; L/day)[e]	0.319	17.0	(0.213, 0.425)	-
Peripheral volume of distribution (V_p; L)[f]	2.53	8.06	(2.13, 2.93)	-
First-order absorption rate constant (k_a; 1/day)	0.107	5.87	(0.0947, 0.119)	-
Absolute bioavailability (F1) after SC administration	0.535	3.14	(0.502, 0.568)	-
Variance of IIV on CL (CV%)	0.0727 (27)	5.31 [8]	(0.0651, 0.0803)	-
Variance of IIV on V_c (CV%)	0.039 (19.7)	8.23 [23]	(0.0327, 0.0453)	-
Variance of IIV on logit F1 (CV%)[g]	0.479 (69.2)	8.18 [16]	(0.402, 0.556)	-
Correlation between IIV of CL and V_c[h]	0.588	9.5	(0.477, 0.698)	-
Correlation between IIV of CL and F1[h]	0.223	19.9	(0.136, 0.311)	-
Correlation between IIV of V_c and F1[h]	0.564	9.9	(0.455, 0.673)	-
Proportional residual error	0.201	2.19	(0.192, 0.21)	-
Additive residual error (µg/mL)	0.0711	20.4	(0.0427, 0.0995)	-

Abbreviations: CI=confidence interval; CL=clearance; CV%=percent coefficient of variation; F1=absolute bioavailability; IIV=interindividual variability calculated as (variance)$^{1/2}$*100 for CV%; k_a=first-order absorption rate constant; PK=pharmacokinetics; Q=intercompartmental clearance; RSE=relative standard error; SC=subcutaneous; SD=standard deviation; V_c=central volume of distribution; V_p=peripheral volume of distribution; η=individual deviation from the population average value; θ=population parameter estimate; ω^2=variance estimate.

[a] [Shrinkage %]; Shrinkage (η)=1-SD(η)/ω

[b] Magnitude of change in the parameter estimate as a result of continuous covariate expressed as a range, ie, percentage change from the median value when the covariate factor varied from the 25th percentile to the 75th percentile of the population.

[c] $$CL\left(\frac{L}{day}\right) = 0.304 \times \left(\frac{Body\ weight}{70}\right)^{0.618} \times \left(\frac{Albumin}{43}\right)^{-1.20} \times \left(\frac{CRP}{6.4}\right)^{0.0281} \times (1.118)^{prior\ biologic\ failture\ status}$$

[d] $$Vc\ (L) = 3.59 \times \left(\frac{Body\ weight}{70}\right)^{0.55}$$

[e] $$Q\left(\frac{L}{day}\right) = 0.319 \times \left(\frac{Body\ weight}{70}\right)^{0.618}$$

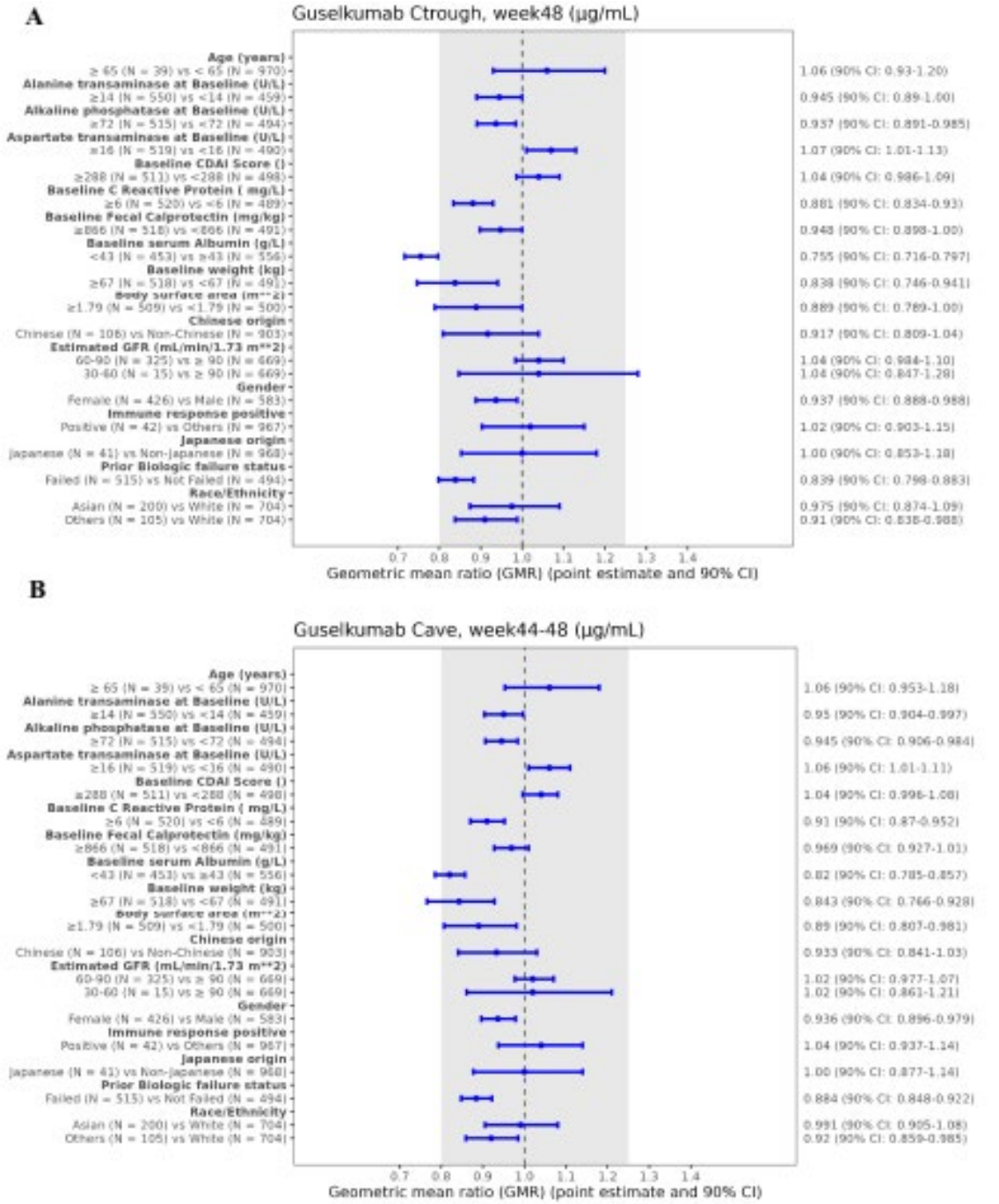
[f] $$Vp\ (L) = 2.53 \times \left(\frac{Body\ weight}{70}\right)^{0.55}$$

[g] Variability of F1 is 0.172 (32.2%) represented as SD (CV%); SD=$(\omega^2_{F1})^{1/2} * \theta_F * (1- \theta_{F1})$; CV%=SD/$\theta_{F1}$ * 100

[h] Correlation=$\frac{cov(\omega^2_{1,1}, \omega^2_{2,2})}{\sqrt{\omega^2_{\ldots}}\sqrt{\omega^2_{\ldots}}}$

The impact of the covariates on guselkumab exposure ($C_{ave,\ week44\text{-}48}$ and $C_{trough,\ week48}$) is presented in Table 3.

Table 3: Multivariate Forest Plots Showing the Impact of Selected Covariates on Steady-state Guselkumab $C_{trough,\ week48}$ (A) and $C_{ave44\text{-}48}$ (B) Using the Final Population PK Model



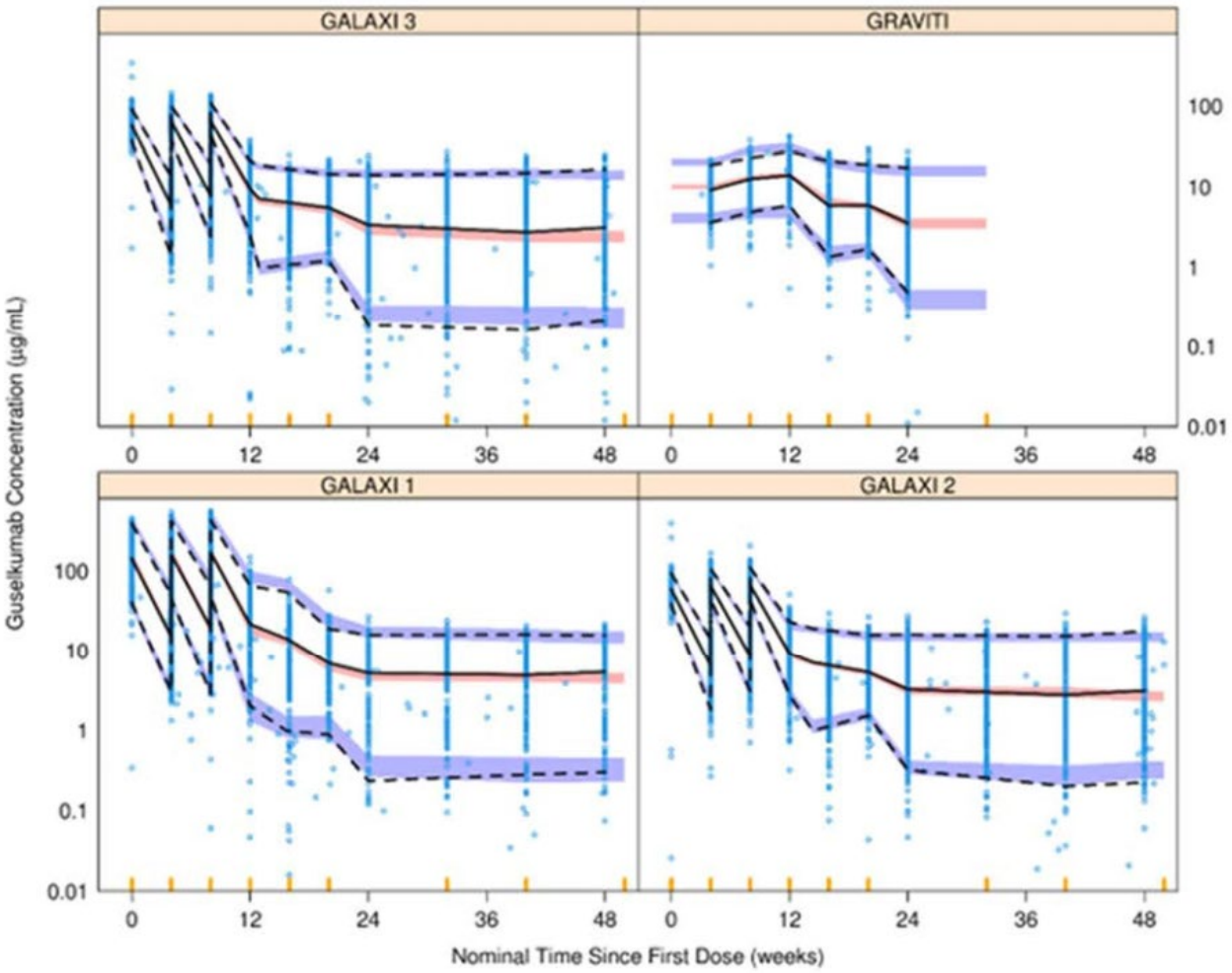
Abbreviations: $C_{ave44\text{-}48}$=average concentration from Week 44 to Week 48; CDAI=Crohn's Disease Activity Index; CI=confidence interval; $C_{trough,\ week48}$=trough concentration at Week 48; GFR=glomerular filtration rate; PK=pharmacokinetic(s).

Note: Vertical dashed line represents the geometric mean ratio of exposure at the reference level or category. The blue lines represent the point estimate and 90% CI. The grey shaded region represents the equivalence range of 0.8 to 1.25 which translates to ±20% difference from the reference level on the normal scale.

Model evaluation

The performance of the final PopPK model was evaluated using visual predictive check (pcVPC, Figure 5).

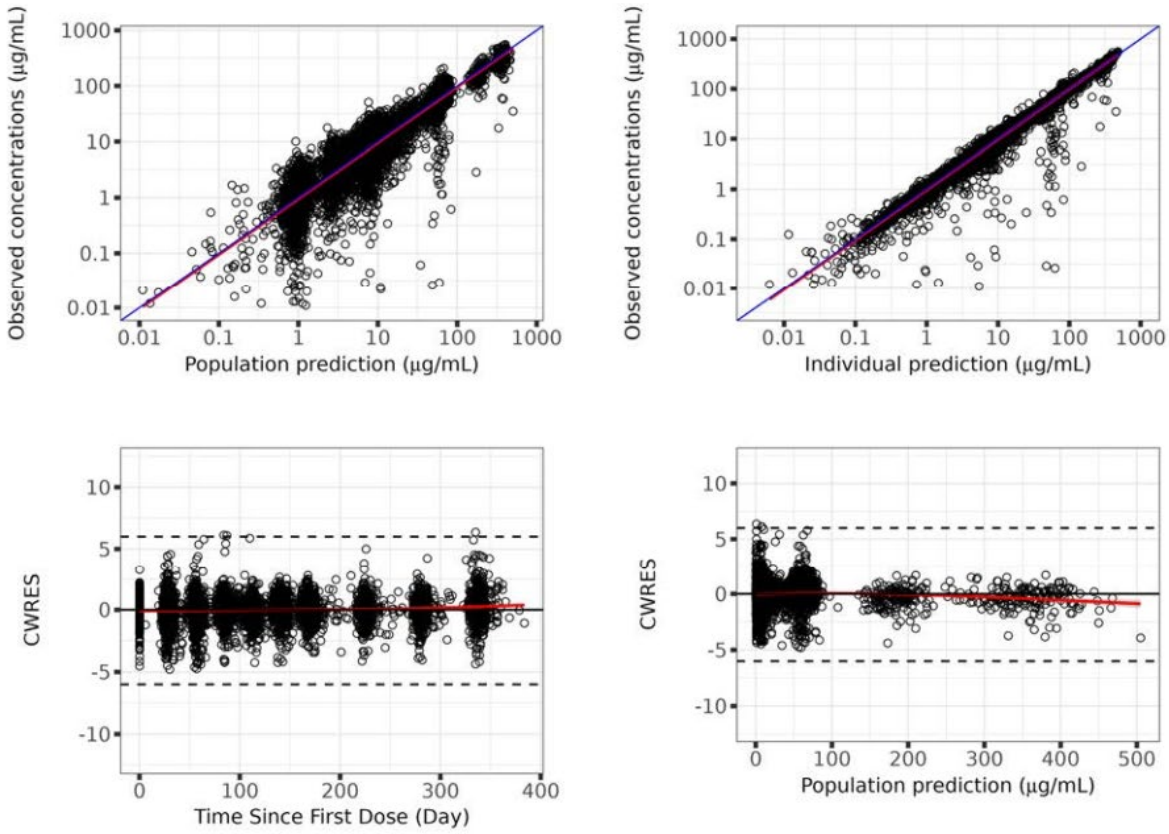
Figure 5: Predicted Corrected Visual Predictive Check (pcVPC) for the Final PopPK Model



CI=confidence interval; PopPK=population pharmacokinetics.
Black solid and dashed lines are the 50th and 5th/95th percentile of the observations. Blue points are observations. Red shaded areas are the 90% CI of the simulated median trend. Blue shaded areas are the 90% CIs of the simulated trends at the 5th and 95th percentiles; n=1,000 replicates.

Goodness-of-fit Diagnostic Plots for PK Base Model are provided in Figure 6.

Figure 6: Goodness-of-fit Diagnostic Plots for PK Base Model (Run7)



Comparative pharmacokinetic analysis, extrinsic and intrinsic factors

This section presents comparisons of PK data across studies and analyses of combined data from GALAXI 1, 2, and 3 through Week 48 and from GRAVITI through Week 24. In addition, comparisons of the PK of guselkumab between the CD indication and the UC indication (the latter based on data from the QUASAR studies).

Galaxi Studies

Following administration of the 200 mg IV q4w induction regimen, serum guselkumab concentrations were similar over time across the 3 GALAXI studies (Table 4).

Table 4: Median Serum Guselkumab Concentrations Through Week 48 Among Participants With CD in the Guselkumab 200 mg IV q4w Induction Treatment Group (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3; PK Analysis Sets)

	Median Guselkumab Concentration (µg/mL)							
	Guselkumab 200 mg IV q4w → 100 mg SC q8w				Guselkumab 200 mg IV q4w → 200 mg SC q4w			
	GALAXI 1	GALAXI 2	GALAXI 3	Combined	GALAXI 1	GALAXI 2	GALAXI 3	Combined
Analysis set: Pharmacokinetics	55	143	143	341	-	146	150	296
Week 0, 1-hour post-administration	53.26	59.87	58.69	58.28	-	57.84	56.48	57.64
Week 4, pre-administration	5.75	7.04	5.80	6.19	-	5.97	6.02	6.01
Week 4, 1-hour post-administration	60.34	67.22	66.00	65.33	-	63.40	63.85	63.51
Week 8, pre-administration	7.79	9.31	8.35	8.46	-	7.99	7.18	7.54
Week 8, 1-hour post-administration	60.61	68.17	66.61	66.61	-	66.06	63.90	65.10
Week 12	8.77	9.23	9.95	9.47	-	9.36	9.26	9.30
Week 16	2.88	2.79	2.74	2.77	-	8.78	8.13	8.48
Week 20	3.29	3.69	3.72	3.65	-	8.37	8.32	8.35
Week 24	0.99	1.08	1.19	1.12	-	8.87	7.98	8.46
Week 32	0.98	0.94	1.02	0.99	-	8.24	8.15	8.22
Week 40	0.96	0.97	0.92	0.95	-	9.04	8.68	8.88
Week 48	1.01	0.99	0.92	0.97	-	8.97	9.69	9.28

Abbreviations: CD=Crohn's disease; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease.
Note: Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

Effect of dose regimen - Exposure Difference Between IV and SC Induction Dose Regimens

Measured data – Induction period

During induction treatment through Week 12, treatment with guselkumab 400 mg SC q4w at Weeks 0, 4, and 8 in GRAVITI resulted in higher trough concentrations of guselkumab than with guselkumab 200 mg IV q4w at Weeks 0, 4, and 8 in the GALAXI studies (combined data) (Table 5).

Table 5: Median Serum Guselkumab Concentrations Through Week 12 (Induction) Among Participants With CD in the Guselkumab 200 mg IV q4w or Guselkumab 400 mg SC q4w Treatment Group (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3, and CNTO1959CRD3004 Phase 3 GRAVITI; PK Analysis Sets)

	Median Guselkumab Concentration (µg/mL)	
	Guselkumab 200 mg IV q4w GALAXI 1/2/3	Guselkumab 400 mg SC q4w GRAVITI
Analysis set: PK analysis set	637	230
Week 4, pre-administration	6.06	9.03
Week 8, pre-administration	8.18	12.55
Week 12	9.42	14.07

Abbreviations: CD=Crohn's disease; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; SC=subcutaneous); SES-CD=Simple Endoscopic Score for Crohn's Disease.
Note: Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

Measured data – Maintenance period

During maintenance treatment through Week 24 in GRAVITI, following 12 weeks of induction treatment with guselkumab 400 mg SC q4w, and in the GALAXI studies (combined data), following 12 weeks of induction treatment with guselkumab 200 mg IV q4w, serum guselkumab concentrations were comparable by Week 24 (Table 6).

Table 6: Median Serum Guselkumab Concentrations From Week 12 Through Week 24 (Maintenance) Among Participants With CD in the Guselkumab 200 mg IV q4w or 400 mg SC q4w Induction Treatment Groups (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3, and CNTO1959CRD3004 Phase 3 GRAVITI; PK Analysis Sets)

	Median Guselkumab Concentration (µg/mL)			
	Guselkumab 200 mg IV q4w Induction	Guselkumab 400 mg SC q4w Induction	Guselkumab 200 mg IV q4w Induction	Guselkumab 400 mg SC q4w Induction
	100 mg SC q8w Maintenance		200 mg SC q4w Maintenance	
	GALAXI 1/2/3	GRAVITI	GALAXI 2/3	GRAVITI
Analysis set: PK analysis set	341	115	296	115
Week 12	9.47	13.84	9.30	14.14
Week 16	2.77	3.97	8.48	9.57
Week 20	3.65	4.25	8.35	9.65
Week 24	1.12	1.23	8.46	9.07

Abbreviations: CD=Crohn's disease; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease.
Note: Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

Simulated data

Simulations were conducted using the parameters of the final POP-PK model to compare the 400 mg SC q4w induction dose regimen in GRAVITI and the 200 mg IV q4w induction regimen employed in the GALAXI studies.

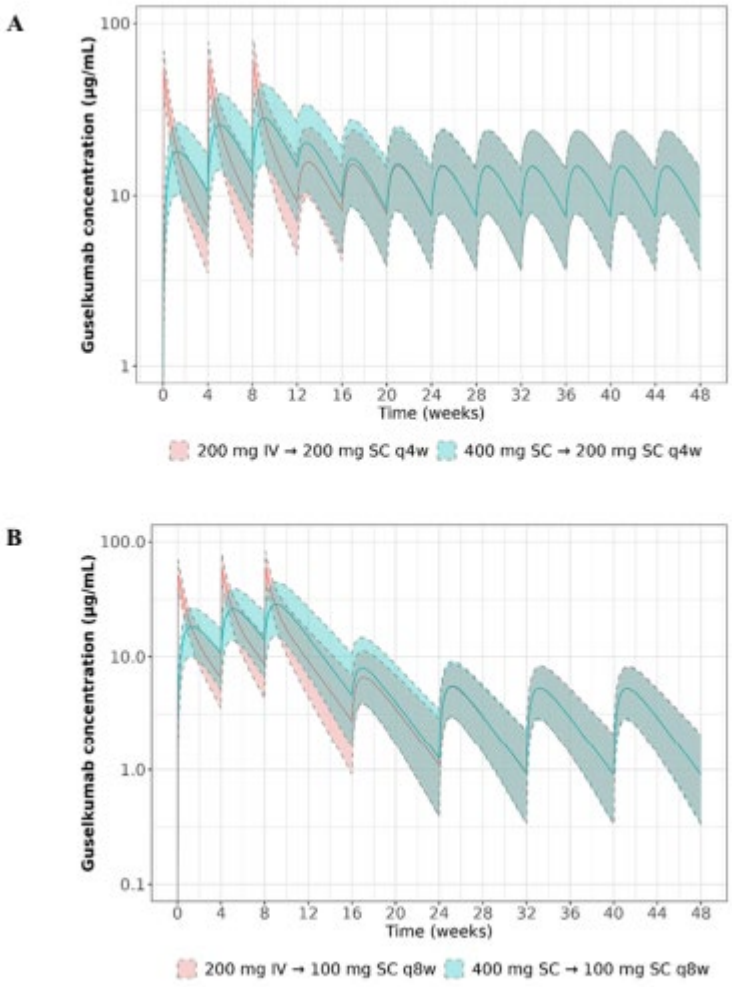
Table 7: Comparison of Model-predicted Guselkumab PK Exposures Following 200 mg IV q4w and 400 mg SC q4w Induction Doses

	GALAXI 200 mg IV q4w (N=622)	GRAVITI 400 mg SC q4w (N=229)
C_{max} (µg/mL)		
Mean (SD)	70.1 (25.1)	27.7 (9.06)
Geometric mean (CV%)	67.6 (25.0)	26.2 (35.5)
Median (range)	65.8 (34.0 - 415)	26.6 (6.20 - 59.2)
$C_{ave,\ week0\text{-}12}$ (µg/mL)		
Mean (SD)	21.4 (7.06)	18.9 (6.47)
Geometric mean (CV%)	20.4 (31.8)	17.8 (37.5)
Median (range)	20.3 (8.26 - 71.6)	18.2 (3.75 - 42.1)
$C_{trough,\ week12}$ (µg/mL)		
Mean (SD)	9.76 (5.38)	14.7 (6.65)
Geometric mean (CV%)	8.28 (67.7)	13.2 (55.1)
Median (range)	8.73 (0.492 - 32.3)	13.8 (1.14 - 38.7)
$AUC_{week0\text{-}12}$ (day*µg/mL)		
Mean (SD)	1,800 (593)	1,590 (543)
Geometric mean (CV%)	1,710 (31.8)	1,490 (37.5)
Median (range)	1,700 (694 - 6,020)	1,530 (315 - 3,540)

Abbreviations: $AUC_{week0\text{-}12}$=area under the concentration-time curve from Week 0 to 12 (induction); $C_{ave,\ week0\text{-}12}$=average concentration from Week 0 to Week 12 (induction); C_{max}=maximum concentration; $C_{trough,\ week12}$=trough concentration at Week 12 (induction); CV%=percent coefficient of variation; IV=intravenous; PK=pharmacokinetic; q4w=every 4 weeks; SC=subcutaneous; SD=standard deviation.
Note: Participants who received all 3 correct induction doses at Weeks 0, 4, and 8 were included in this statistics summary.

The simulated guselkumab concentration-time profiles through Week 48 after the administration of guselkumab 200 mg IV q4w or 400 mg SC q4w in the induction period, followed by the same maintenance SC dose regimen, is presented in Figure 7.

Figure 7: Simulated Guselkumab PK Profiles Over 48 Weeks Comparing 200 mg IV q4w and 400 mg SC q4w in the Induction Period Followed by 200 mg SC q4w (A) or 100 mg SC q8w (B) Maintenance Treatment



Abbreviations: CD=Crohn's disease; CRP=C-reactive protein; IV=intravenous; PK=pharmacokinetic(s); q4w=eve
4 weeks; q8w=every 8 weeks; SC=subcutaneous.
Note: Solid line represents the median and the shaded area represents the 90% prediction interval.

Effect of Body Weight

Based on combined data from the GALAXI studies, in the respective guselkumab treatment group, median serum guselkumab concentrations tended to decrease with increasing body weight quartile subgroups (Figure 8).

Figure 8: Median Serum Guselkumab Concentrations (µg/mL) Through Week 48 by Body Weight Quartiles Among Participants With CD in the Guselkumab 200 mg IV q4w Treatment Group (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3; PK Analysis Set)

	Guselkumab 200 mg IV q4w → 100 mg SC q8w				Guselkumab 200 mg IV q4w → 200 mg SC q4w			
	< 1st Quartile[a]	≥1st and <2nd Quartile[a]	≥2nd and <3rd Quartile[a]	≥3rd Quartile[a]	< 1st Quartile[a]	≥1st and <2nd Quartile[a]	≥2nd and <3rd Quartile[a]	≥3rd Quartile[a]
Analysis set: Pharmacokinetics	85	85	84	87	74	74	74	74
Week 0, 1-hour post-administration	72.76	60.77	53.96	51.73	65.87	57.91	54.80	52.39
Week 4, pre-administration	7.03	6.97	5.43	5.53	5.66	6.07	6.16	5.89
Week 4, 1-hour post-administration	77.53	68.35	58.58	55.99	74.72	67.12	61.91	56.21
Week 8, pre-administration	9.62	9.22	7.38	8.19	7.01	7.67	9.17	7.17
Week 8, 1-hour post-administration	81.43	72.97	60.87	58.50	78.30	67.17	62.94	57.83
Week 12	11.27	10.95	8.60	8.90	9.14	10.97	10.70	8.21
Week 16	3.25	3.07	2.55	2.75	9.26	10.47	8.15	6.64
Week 20	4.80	3.69	3.44	3.18	9.30	9.88	8.37	6.63
Week 24	1.58	1.05	0.89	1.07	9.45	10.63	7.43	6.64
Week 32	1.13	1.13	0.89	0.96	10.08	9.67	7.66	6.73
Week 40	1.29	1.11	0.77	0.79	10.33	11.00	8.86	6.77
Week 48	1.26	0.96	0.86	0.86	12.08	11.30	8.62	5.83

Abbreviations: CD=Crohn's disease; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease.

Note: Includes only participants with SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease] at baseline.

Note: Concentrations below the lowest quantifiable concentration (ie, <0.01 µg/mL) were treated as zero in calculating the summary statistics.

[a] Body weight quartiles are based on participants in each treatment group as follows:
Guselkumab 200 mg IV q4w → 100 mg SC q8w: 1st quartile = 55.90 kg, 2nd quartile = 66.20 kg, 3rd quartile = 78.00 kg.
Guselkumab 200 mg IV q4w → 200 mg SC q4w: 1st quartile = 55.45 kg, 2nd quartile = 65.95 kg, 3rd quartile = 78.35 kg.

The impact of body weight on guselkumab concentration was not considered clinically relevant because there was no observed impact on efficacy.

Effect of Biologic Failure Status

Based on combined data from the GALAXI studies, in the respective guselkumab treatment group, median guselkumab concentrations tended to be lower in BIO-Failure participants compared with CON-Failure participants (Table 8).

Table 8: Median Serum Guselkumab Concentrations Through Week 48 by Biologic Failure Status Among Participants With CD (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3; PK Analysis Sets)

	Median Guselkumab Concentration (µg/mL)			
	Guselkumab 200 mg IV q4w → 100 mg SC q8w		Guselkumab 200 mg IV q4w → 200 mg SC q4w	
	BIO-Failure	CON-Failure	BIO-Failure	CON-Failure
Analysis set: PK analysis set	181	160	147	149
Week 0, 1 hour post-administration	57.84	58.40	57.38	58.16
Week 4, pre-administration	5.35	7.47	5.26	6.43
Week 4, 1 hour post-administration	62.10	67.70	63.88	63.36
Week 8, pre-administration	7.29	10.21	6.64	9.13
Week 8, 1 hour post-administration	64.58	70.43	63.10	67.31
Week 12	8.21	10.78	8.09	11.02
Week 16	2.16	3.45	7.96	8.78
Week 20	3.03	4.35	8.06	9.63
Week 24	0.88	1.44	8.30	8.86
Week 32	0.77	1.20	8.03	8.25
Week 40	0.70	1.14	8.67	9.04
Week 48	0.80	1.22	8.54	9.75

Abbreviations: BIO-Failure=biologic therapy failure or intolerance; CD=Crohn's disease; CON-Failure=conventional therapy failure or intolerance; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease.
Note: Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

Effect of Baseline Immunomodulator Use

Based on combined data from the GALAXI studies, in the respective guselkumab treatment groups, the median guselkumab concentrations were similar between participants receiving concomitant immunomodulators (ie, AZA, 6-MP, MTX) at baseline compared with those not receiving immunomodulators. This observation is consistent with the lack of impact of concomitant immunomodulators on guselkumab CL in the population PK analysis.

Effect of disease - Comparison of Serum Guselkumab Concentrations Between Participants With Crohn's Disease or Ulcerative Colitis

The comparison of serum guselkumab concentrations between participants with CD (GALAXI studies) and UC (QUASAR studies) was based on the corresponding timepoints through Week 48 across the 2 programmes. In the GALAXI studies, weeks are labelled Week 0 through Week 48, whereas in the CNTO1959UCO3001 study, the weeks are labelled Week I-0 through Week I-12 (12 weeks induction), and Week M-0 through Week M-36 (36 weeks maintenance) for a total of 48 weeks of continuous treatment with guselkumab. To compare the data, the weeks were mapped to represent comparable

timepoints, eg, Week 12 and Week M-0 both represent data after 12 weeks of treatment, and Week 48 and Week M-36 both represent data after 48 weeks of treatment.

Induction

Following the 200 mg IV q4w induction dose regimen in the combined GALAXI and combined QUASAR induction studies, median and mean guselkumab concentrations were similar over time during induction between participants with CD and UC (Table 9).

Table 9: Median Serum Guselkumab Concentrations Through Week 12 Among Participants With Inflammatory Bowel Disease (CD or UC); PK Analysis Set for Participants who Received Guselkumab 200 mg IV q4w Prior to Week 12 (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3, and CNTO1959UCO3001 Phase 2b Induction Study 1 and Phase 3 Induction Study 2)

	Median Guselkumab Concentration (µg/mL) Guselkumab 200 mg IV q4w		
	CD[a]	UC[b]	Combined
Analysis set: PK analysis set [c]	637	522	1159
Week 0/I-0, 1-hour post administration	57.84	59.90	58.98
Week 4/I-4, pre-administration	6.06	5.78	5.92
Week 4/I-4, 1-hour post administration	64.57	65.04	64.78
Week 8/I-8, pre-administration	8.18	8.09	8.12
Week 8/I-8, 1-hour post administration	65.89	66.26	66.14
Week 12/I-12	9.42	9.45	9.44

Abbreviations: CD=Crohn's disease; I=Induction; IV=intravenous; PK=pharmacokinetic(s); q4w=every 4 weeks; SES-CD=Simple Endoscopic Score for Crohn's Disease; UC=ulcerative colitis.

[a] CNTO1959CRD3001 studies GALAXI 1 (Phase 2b), GALAXI 2 (Phase 3) and GALAXI 3 (Phase 3). Includes data from Week 0 (mapped to Week I-0) through Week 12 (mapped to Week I-12). Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

[b] CNTO1959UCO3001 induction studies 1 (Phase 2b) and 2 (Phase 3). Includes data from Week I-0 through Week I-12. Includes only participants with modified Mayo score 5 to 9 at induction baseline.

[c] PK analysis set for participants who received Guselkumab 200 mg IV q4w prior to Week 12.

Maintenance

Following the same SC maintenance dose regimens, guselkumab concentrations were similar between participants with CD and participants with UC (Table 10).

Table 10: Median Serum Guselkumab Concentrations From Week 12 Through Week 48 Among Participants With Inflammatory Bowel Disease (CD or UC); PK Analysis Set Participants who Were Responders to Guselkumab 200 mg IV q4w Induction Treatment and Were Assigned to Guselkumab SC Treatment Groups in Maintenance (CNTO1959CRD3001 Phase 2 GALAXI 1, Phase 3 GALAXI 2, and Phase 3 GALAXI 3, and CNTO1959UCO3001 Phase 3 Maintenance Study)

	Median Guselkumab Concentration (µg/mL)						
	Guselkumab 200 mg IV q4w Induction →						
	Guselkumab 100 mg SC q8w			Guselkumab 200 mg SC q4w			
	CD[a]	UC[b]	Combined	CD[a]	UC[b]	Combined	Total
Analysis set: PK analysis set[c]	219	166	385	189	168	357	742
Week 12/M-0	9.73	10.89	10.13	10.26	10.32	10.27	10.26
Week 16/M-4	2.97	2.94	2.95	8.98	8.68	8.88	5.31
Week 20/M-8	3.75	4.08	3.88	8.44	8.38	8.43	5.86
Week 24/M-12	1.14	1.29	1.20	8.50	8.82	8.71	3.26
Week 32/M-20	1.05	1.03	1.04	8.75	8.93	8.91	3.23
Week 40/M-28	1.00	1.00	1.00	9.02	9.27	9.08	3.00
Week 48/M-36	1.02	1.06	1.05	10.00	8.71	9.30	3.04

Abbreviations: CD=Crohn's disease; IV=intravenous; IWRS=interactive web response system; M=maintenance; PK=pharmacokinetic(s); q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; UC=ulcerative colitis.

Note: Responder participants were in clinical response as assessed by IWRS.

Note: Guselkumab 100 mg SC q8w: Participants received guselkumab 100 mg SC q8w starting at Week 16/M-4 through Week 48/M-36 at scheduled guselkumab administration visits (ie, Weeks 16/M-4, 24/M-12, 32/M 20, 40/M-28, and 48/M 36).

Guselkumab 200 mg SC q4w: Participants received guselkumab 200 mg SC q4w starting at Week 12/M-0 through Week 48/M-36 (ie, Weeks 12/M-0, 16/M-4, 20/M-8, 24/M-12, 28/M-16, 32/M-20, 36/M-24, 40/M 28, 44/M-32, and 48/M-36).

[a] CNTO1959CRD3001 studies GALAXI 1 (Phase 2b), GALAXI 2 (Phase 3) and GALAXI 3 (Phase 3). Includes data from Week 12 (mapped to Week M-0) through Week 48 (mapped to Week M-36). Includes only participants with SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease) at baseline.

[b] CNTO1959UCO3001 maintenance study (Phase 3). Includes data from Week M-0 through Week M-36, or up to the time of dose adjustment (occurred from Week M-8 through Week M-32) for participants who had a dose adjustment from 100 mg q8w to 200 mg q4w. Includes only participants with modified Mayo score 5 to 9 at induction baseline.

[c] PK analysis set for participants with CD or UC who were responders to Guselkumab 200 mg IV q4w induction treatment and were assigned to Guselkumab SC treatment groups in maintenance.

Comparison of Population Pharmacokinetic Parameters Between Participants With Crohn's Disease and Participants With Ulcerative Colitis

The PK parameters estimated from the population PK analyses of guselkumab in participants with CD vs UC are summarized in Table 11.

Table 11: Comparison of Parameter Estimates From the Final Population PK Model for Participants With Inflammatory Bowel Disease (CD or UC)

Parameter (Unit)	CD	UC	Difference
CL (L/day)	0.304	0.312	2.6%
V_c (L)	3.59	3.38	5.9%
V_p (L)	2.53	2.58	2.0%
Q (L/day)	0.319	0.298	6.6%
k_a (1/day)	0.107	0.123	15.0%
F1 (%)	53.5	58.8	9.9%
$T_{1/2}$ (day)	16.8	16.5	1.8%

Abbreviations: CD=Crohn's disease; CL=clearance; F1=absolute SC bioavailability; k_a=first-order absorption rate constant; PK=pharmacokinetic(s); Q=intercompartmental clearance; $T_{1/2}$=terminal elimination half-life; UC=ulcerative colitis; V_c=central volume of distribution; V_p=peripheral volume of distribution.

Note: Difference was calculated as: 100*(CD parameter - UC parameter)/CD parameter.

With respect to factors associated with guselkumab PK, similar covariates such as body weight, albumin, CRP, and prior biologic failure status were found to influence the PK of guselkumab in both CD and UC.

2.3.3. Pharmacodynamics

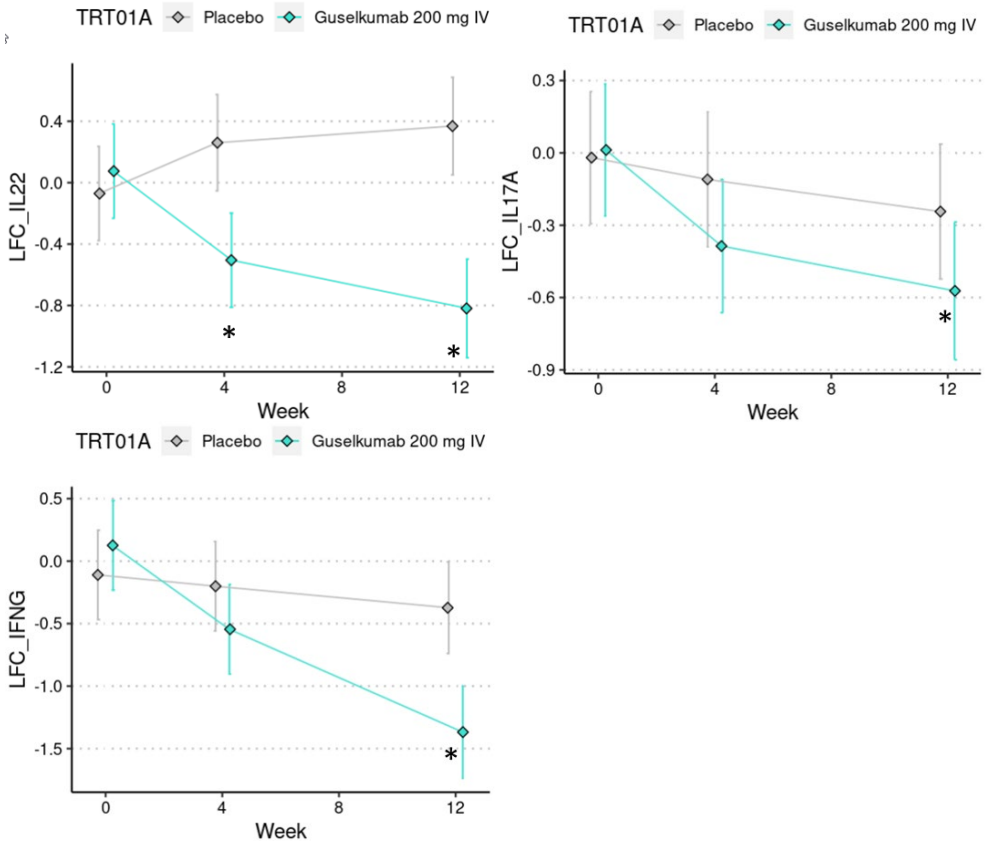
Biomarkers

The primary objective of the exploratory biomarker analysis was to utilize tissue biopsy and serum samples from participants in GALAXI 1 up to Week 12.

Serum Biomarkers

Serum proteomic profiling demonstrated that there was a significant reduction of IL-23-dependent proinflammatory cytokine profiles in response to guselkumab, relative to placebo, as early as Week 4 which continued to decline through Week 12. Analysis of selected serum protein levels confirmed that IL-23-dependent pharmacodynamic biomarkers IL-22, IL-17A, and IL-17F showed significant reduction upon guselkumab treatment (Figure 9).

Figure 9: Treatment Effects of Serum IL-22, IL-17A, and IFNγ Protein Markers at Week 4 vs Week 0 and Week 12 vs Week 0



Abbreviations: IFNγ (or IFNG)=interferon gamma; IL=interleukin; IV=intravenous; LFC=Log fold change.

Statistical model: Treatment vs Baseline contrasts per treatment, with subject random effect; * notes nominal p <0.05.

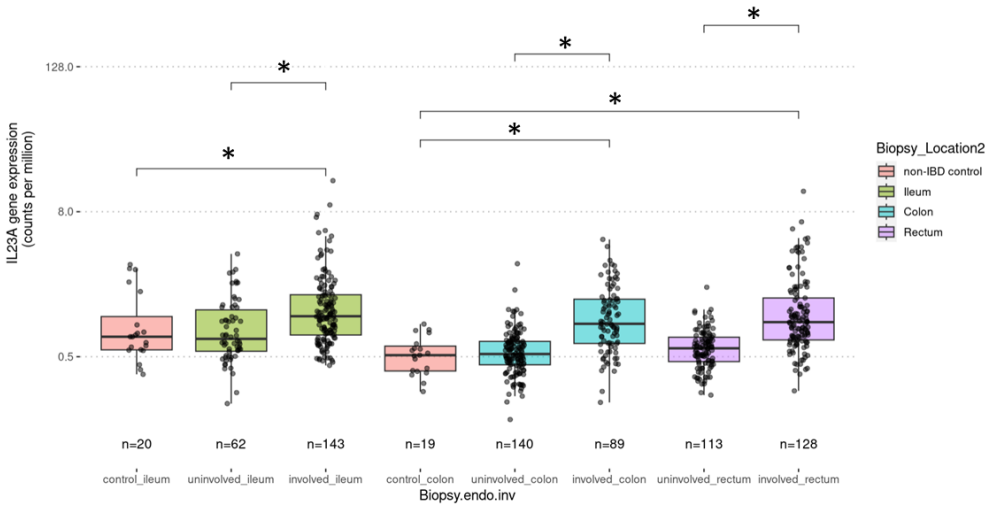
Tissue Transcriptomics

Mucosal biopsy samples were collected from all participants during the scheduled ileocolonoscopy visits at 3 locations: terminal ileum, splenic flexure, and rectum (within 10 cm of anal verge), as specified in the study protocol for GALAXI 1, to study the effect of study intervention on gene and protein expression and for histological assessment of disease and healing.

For differential gene expression analysis, representative samples were identified per region by using a filter of baseline samples that had >0 segment SES-CD. These baseline samples were then tracked over time to represent longitudinal treatment effect changes per treatment arm with biopsy region as a fixed effect and participant as a random effect. The remainder of "uninvolved" samples and non-IBD control ileal and colonic samples were also included for comparison.

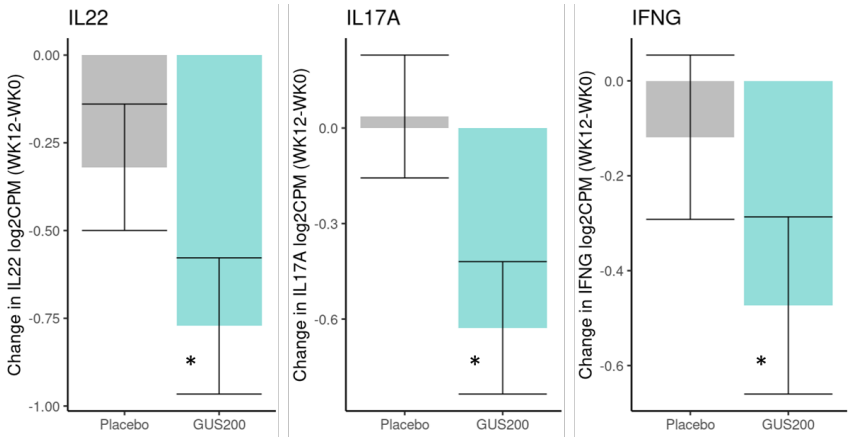
IL-23 pathway-associated genes IL-22, IFNγ, and IL-17A were reduced relative to pre-treatment levels and the colonic tissue expression of these PD markers was substantially reduced upon exposure to guselkumab (Figure 10).

Figure 10: IL-23p19 (IL23A) Gene Expression in CD Colon and Ileum Tissue at Baseline Relative to Uninvolved Colon and Ileum and Non-IBD Control Tissue



Abbreviations: CD=Crohn's disease; IBD=inflammatory bowel disease; IL=interleukin; ns=not significant. Note: t-test group contrasts: * = nominal p≤0.05.

Figure 11: Individual Effects Plots of IL-22, IFNγ, and IL-17A Gene Expression Profiles in CD Colonic and Ileal Tissue as Determined by RNAseq

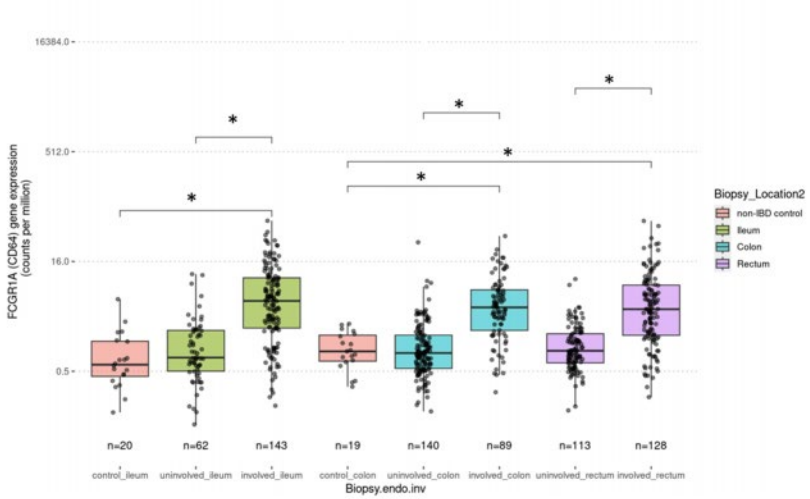


Abbreviations: CD=Crohn's disease; GUS200=Guselkumab 200 mg IV q4w; IFNγ (or IFNG)=interferon gamma; IL=interleukin; IV=intravenous; RNAseq=ribonucleic acid sequencing; WK=week.

Note: Placebo baseline (n=91), WK12 (n=77). Guselkumab 200 mg IV baseline (n=73), WK12 (n=73). Statistical model: Treatment vs Baseline contrasts per treatment, Biopsy region as fixed effect with participant random effect.

Note: t-test group contrasts: * = nominal p≤0.05.

Figure 12: FCGR1A (CD64) gene expression in CD colon and ileum tissue at baseline relative to uninvolved colon and ileum and non-IBD control tissue.



Abbreviations: CD=Crohn's Disease; IBD=inflammatory bowel disease; ns=not significant.
t-Test group contrasts: *: nominal p≤0.05.

Immunogenicity

GALAXI Studies

Induction

Among participants who received the guselkumab 200 mg IV q4w induction regimen across the 3 GALAXI studies, the incidence of antibodies to guselkumab through Week 12 was 1.3% (8 of 634 participants), ranging between 0% and 2.4% in the individual GALAXI studies. Most participants were positive for antibodies (7 of 8 participants). Of the 8 participants with antibodies to guselkumab through Week 12, 1 (12.5%) was positive for NAbs through Week 12, corresponding to 0.2% (1 of 634 participants) of participants treated with guselkumab.

Maintenance

Among participants who received the guselkumab 200 mg IV q4w induction regimen followed by 100 mg SC q8w or 200 mg SC q4w for maintenance across the 3 GALAXI studies, the incidence of antibodies to guselkumab through Week 48 was 4.7% (30 of 634 participants), ranging between 0% and 7.2% in the individual GALAXI studies. Most participants who were positive for antibodies (24 of 30 participants) had a low peak titer (1:11.25). The incidence of antibodies to guselkumab was similar between participants receiving 100 mg SC q8w (4.4%) and 200 mg SC q4w (5.1%). Of the 30 participants with antibodies to guselkumab through Week 48, 2 (6.7%) had NAbs, corresponding to 0.3% (2 of 634 participants) of participants treated with guselkumab.

GRAVITI study

Through Week 12, of the 230 participants who received guselkumab and had appropriate samples for antibodies, 2 (0.9%) participants were positive for antibodies, neither of which were neutralizing.

Among the 273 participants who received guselkumab at any time through Week 48 (including participants who were initially receiving placebo and were rescued with guselkumab) and had appropriate samples, 24 (8.8%) participants developed antibodies to guselkumab. Of the 24 participants who developed antibodies to guselkumab, 3 (12.5%) were positive for Nabs.

Comparison of Incidence of Antibodies to Guselkumab in GALAXI Studies With GRAVITI

Through Week 12, the incidence of antibodies to guselkumab was 1.3% [8 of 634 participants] in the combined GALAXI studies, ranging between 0.0% and 2.4% in individual studies, and 0.9% [2 of 230 participants] in GRAVITI, resulting in an overall incidence of 1.2% through Week 12 across the 4 studies.

Through Week 24, the incidence of antibodies to guselkumab was 1.4% [9 of 634 participants] in the combined GALAXI studies, ranging between 0.0% and 2.8% in individual studies, and 3.5% [8 of 230 participants] in GRAVITI, resulting in an overall incidence of 2.0% through Week 24 across the 4 studies.

At both timepoints and in all studies, most participants had a low peak titer of 1:11.25.

Consistent with the low incidence of NAbs in GALAXI, none of the participants with antibodies to guselkumab through Week 24 in GRAVITI were positive for NAbs.

Incidence of Antibodies to Guselkumab by Baseline Immunomodulator Use

Through Week 48 in the combined GALAXI studies, the incidence of antibodies to guselkumab was numerically higher among participants without baseline immunomodulator use (5.7%, 25 of 437 participants) compared with those with baseline immunomodulator use (2.5%, 5 of 197 participants). A similar pattern was observed in GRAVITI with an incidence of 4.3% (7 of 164 participants) and 1.5% (1 of 66 participants) through Week 24 among those without and with baseline immunomodulator use, respectively.

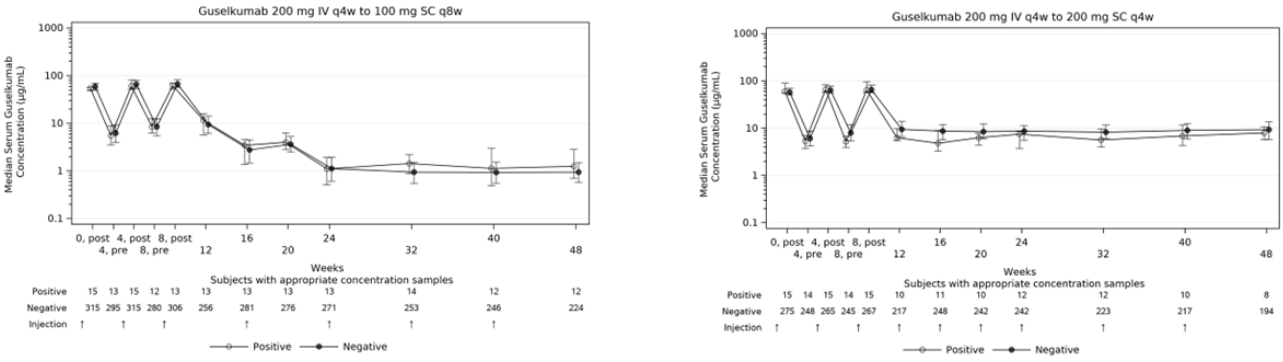
Effect of Immunogenicity on Guselkumab Pharmacokinetics

The median serum guselkumab concentrations were generally similar among participants who were positive or negative for antibodies to guselkumab in the guselkumab 100 mg SC q8w maintenance group (combined GALAXI studies) and in the guselkumab 200 mg SC q4w maintenance treatment group (combined GALAXI 2 and GALAXI 3 studies; Figure 13).

Among participants with available data, the average steady-state trough concentrations were generally similar before and after the first positive antibody to guselkumab sample.

In the population PK analysis, the presence of antibodies to guselkumab was not found to have an impact on the CL of guselkumab.

Figure 13: Median (Interquartile Range) Serum Guselkumab Concentrations (µg/mL) Through Week 48 by Antibody to Guselkumab Status Through Week 48 Among Participants in Galaxi studies, PK Analysis Set)



Note: Participants positive for antibodies to guselkumab includes all participants who were positive (treatment-boosted or treatment-induced) at any time after their first guselkumab administration through Week 48.

Effect of Immunogenicity on Efficacy

The proportion of participants achieving multiple efficacy outcomes was similar among participants who were positive for antibodies to guselkumab compared with participants who were negative through Week 48 in the GALAXI studies.

Effect of Immunogenicity on Safety

The development of antibodies to guselkumab did not have an impact on AEs within 1 hour of infusion or on injection site reactions.

2.3.4. PK/PD modelling

Exposure-response (E-R) Model Development

The E-R analyses were conducted to examine the relationship between systemic guselkumab exposure and selected clinical efficacy endpoints. These analyses were based on data from randomized participants in GALAXI 1, 2, and 3, and GRAVITI who received at least 1 dose of guselkumab or placebo, and satisfied the SES-CD criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).

For the induction E-R analyses at Week 12, a total of 950 participants from the GALAXI studies were included, with 203 participants treated with placebo, 637 treated with guselkumab 200 mg IV q4w, and 56 and 54 treated with guselkumab 600 mg and 1200 mg IV q4w, respectively.

For the maintenance E-R modeling analyses at Week 48, a total of 904 participants from the GALAXI studies were included, with 191 participants treated with placebo, 326 participants treated with guselkumab 100 mg SC q8w, and 387 participants treated with 200 mg guselkumab SC q4w.

The numbers of participants included in the E-R analysis for induction through Week 12 and for maintenance through Week 24 are summarized in Table 12.

Table 12: Summary of Participants Included in the Graphical Assessments of Comparative Exposure-response Analyses Between IV (GALAXI) and SC (GRAVITI) Induction Treatment

	GALAXI	GRAVITI	Overall
Week 12, n	785	347	1,132
Placebo	148	117	265
200 mg IV q4w	637	0	637
400 mg SC q4w	0	230	230
Week 24, n	748	330	1,078
Placebo	138	103	241
100 mg SC q8w	326	114	440
200 mg SC q4w	284	113	397

Abbreviations: IV=intravenous; n=number of participants included in the analysis; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous.

The E-R modeling was a sequential 2-step process where actual dosing information was used in the final population PK model to derive individual exposures (C_{trough} or C_{ave}), which were then used to conduct exploratory E-R analyses, and to develop E_{max} logistic regression models to quantify the

relationship between guselkumab exposure and the probability of achieving each of the binary clinical endpoints. In these models, the drug effect for guselkumab was modeled as:

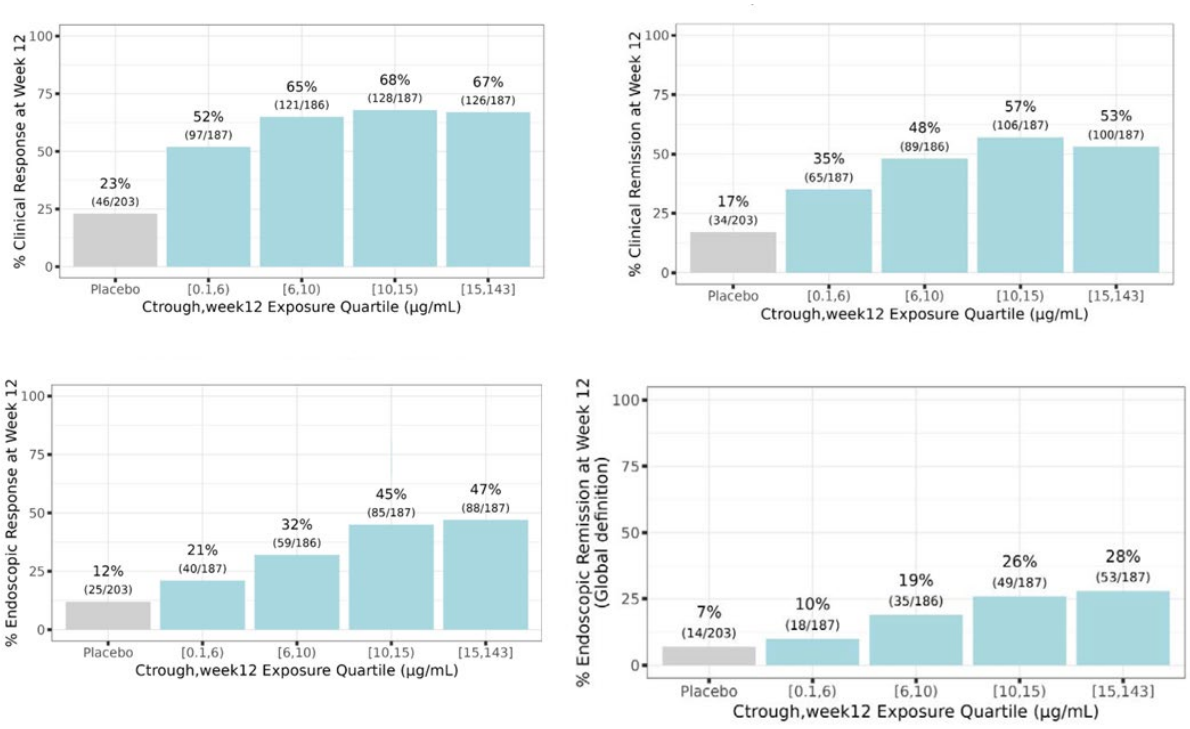
$$\text{logit}\,[\text{prob(achieving endpoint)}] = \alpha + \text{E}_{\max} \times \frac{\text{EM}}{(\text{EM} + \text{EC}_{50})}$$

where $\text{logit}(x) = \log\left[\frac{x}{(1-x)}\right]$; a is the intercept (efficacy response in the absence of drug exposure); EM is the exposure metric; E_{max} is the maximum drug effect and EC_{50} is the exposure metric level corresponding to 50% of the maximum drug effect (ie, half-maximal drug effect).

Exposure-response Analysis for Induction Efficacy

Although there was a lack of dose-response and E-R relationships of guselkumab IV induction in participants with CD in the Phase 2 study (GALAXI 1, doses of 200, 600, and 1200 mg), initial exploratory E-R analyses from combined data across all 3 studies (GALAXI 1, GALAXI 2, and GALAXI 3) suggested apparent positive E-R relationships between $C_{trough,\ week12}$ and efficacy endpoints at Week 12 (clinical response, clinical remission, endoscopic response, endoscopic remission) (Figure 14).

Figure 14: Proportion of Responders in Participants with CD for Each Efficacy Endpoint at Week 12 by Serum Guselkumab Ctrough,week12 Quartiles (Pooled Data from GALAXI 1, GALAXI 2, and GALAXI 3)



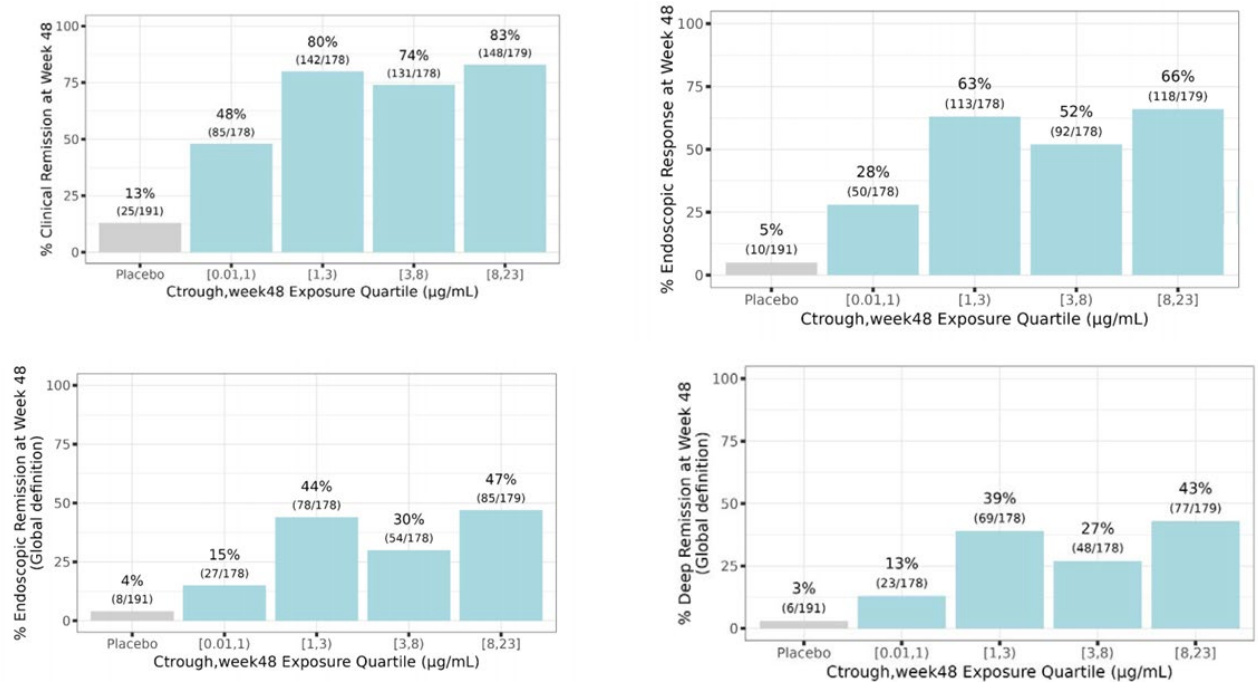
Because there was no dose-response observed across these efficacy endpoints, it was hypothesized that the intrinsic disposition characteristics of guselkumab ($T_{1/2}$ or CL), as opposed to the level of exposure to guselkumab, were associated with the response of individual participants to the treatment. Further analyses confirmed that participants with slower CL (longer $T_{1/2}$) tended to respond better to guselkumab regardless of dose. However, when this relationship was plotted and stratified by dose groups, then the apparent relationship between half-life and response rates disappeared.

Exposure-response Analysis for Maintenance Efficacy

Similar to induction, initial E-R analysis also suggested positive E-R relationships between $C_{trough,\ week48}$ (ie, at steady state) and efficacy endpoints at Week 48 (clinical remission, endoscopic response,

endoscopic remission, and deep remission) following maintenance treatment with guselkumab in the GALAXI studies.

Figure 15: Proportions of Responders in Participants with CD for Each Efficacy Endpoint at Week 48 by Serum Guselkumab Ctrough, week48 Quartiles (Pooled Data from GALAXI 1, GALAXI 2, and GALAXI 3)



For all evaluated efficacy endpoints at Week 48, $C_{trough,\ week48}$ was a better predictor for the E-R relationships than $C_{ave,\ week40\text{-}48}$.

Clinical Remission at Week 48

Covariate analysis indicated that clinical remission status at Week 12 (at the end of induction), endoscopic response status at Week 12, and prior biologic failure status had significant effects on the E-R relationship between steady-state $C_{trough,\ week48}$ and clinical remission at Week 48. Of these, the most influential covariate in the E-R model of clinical remission at Week 48 was the clinical remission status at Week 12. The model indicates that participants who achieved clinical remission at Week 12 tended to have a higher probability of still being in clinical remission at Week 48 compared with those who were not in clinical remission at Week 12.

From the model predictions, for those in clinical remission at Week 12, and irrespective of endoscopic response status at Week 12, a high proportion of participants (>88%) were predicted to still be in clinical remission at Week 48 with no substantial differences between the maintenance dose regimens. On the other hand, among participants who were not in clinical remission at Week 12, the higher 200 mg SC q4w maintenance dose regimen was predicted to result in a greater proportion of participants achieving clinical remission at Week 48 compared with the 100 mg SC q8w regimen.

Endoscopic Response at Week 48

Covariate analysis indicated that endoscopic response status at Week 12, clinical response status at Week 12, CRP >5 mg/L status at Week 12, and baseline SES-CD score >12 status had statistically significant effects on the E-R relationship between steady-state $C_{trough,\ week48}$ and endoscopic response at Week 48. Of these, the baseline SES-CD score >12 status and endoscopic response status at Week 12 were considered the most influential covariates in the E-R model of endoscopic response at Week 48.

Model predictions suggested that for participants with baseline SES-CD score >12 who achieved endoscopic response at Week 12, a high proportion (>77%) were likely to remain in endoscopic response at Week 48, regardless of the maintenance dose regimen. In the other 3 subgroups, the 200 mg SC q4w regimen was predicted to result in greater proportions of participants achieving endoscopic response at Week 48 compared with the 100 mg SC q8w regimen.

Table 13: Model-predicted Week 48 Response Rates for SC Maintenance Treatment Groups - Stratified by Covariates

Response Variable at Week 48	Covariates		Response Rate (%) (95% CI)			
Clinical Remission	Clinical Remission at Week 12	Endoscopic Response at Week 12	100 mg SC q8w		200 mg SC q4w	
			Observed	Predicted	Observed	Predicted
	Yes	Yes	87.7	93.4 (85.2-98.6)	92.7	96.2 (89.7-100)
	Yes	No	81.2	84.5 (75.3-92.4)	86.0	90.2 (82.1-96.1)
	No	Yes	74.0	70.4 (55.1-85.1)	78.2	79.6 (65.8-91.8)
	No	No	42.6	45.5 (35.7-58.1)	49.3	58.9 (47.5-69.8)
Endoscopic Response	Baseline SES-CD >12 score	Endoscopic Response at Week 12	100 mg SC q8w		200 mg SC q4w	
			Observed	Predicted	Observed	Predicted
	Yes	Yes	84.6	74.0 (61.7-84.6)	85.3	82.2 (71.0-91.2)
	No	Yes	72.7	73.7 (62.0-86.4)	66.1	81.7 (70.1-90.9)
	Yes	No	39.2	31.4 (21.0-44.0)	55.3	45.5 (33.7-57.3)
	No	No	25.9	35.4 (25.2-46.1)	33.3	47.2 (36.9-56.6)

CI=confidence interval; $C_{trough, week48}$=trough concentration at Week 48 (maintenance); E-R=exposure-response; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease.
Predicted response rates were calculated based on 1000 trial simulations including variability in concentrations and uncertainty of parameter estimates of the E-R models.

Figure 16: Model-predicted E-R Relationships for Clinical Remission at Week 48 Using $C_{trough, week48}$ as the PK Exposure Metric in Participants With CD, Stratified by Clinical Remission at Week 12 and Endoscopic Response at Week 12; Achieving Week 12 Clinical Remission (A) and Not Achieving Week 12 Clinical Remission (B)

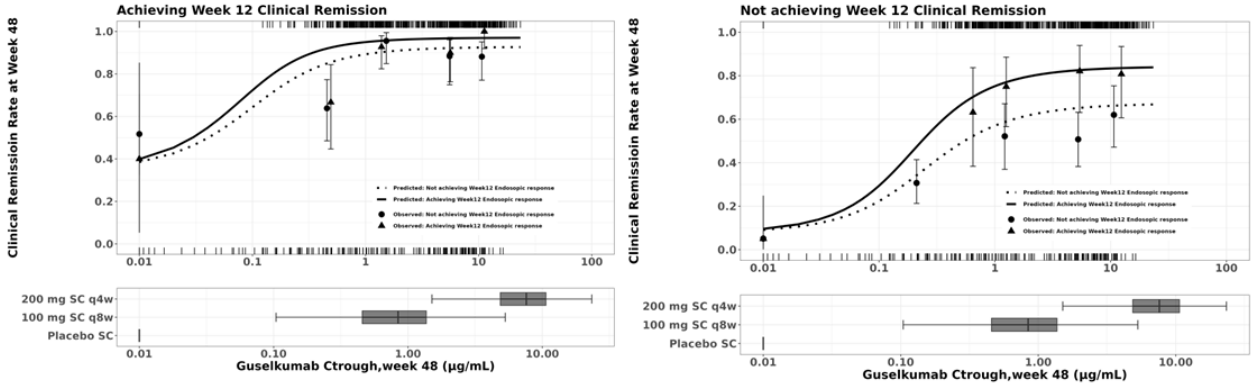
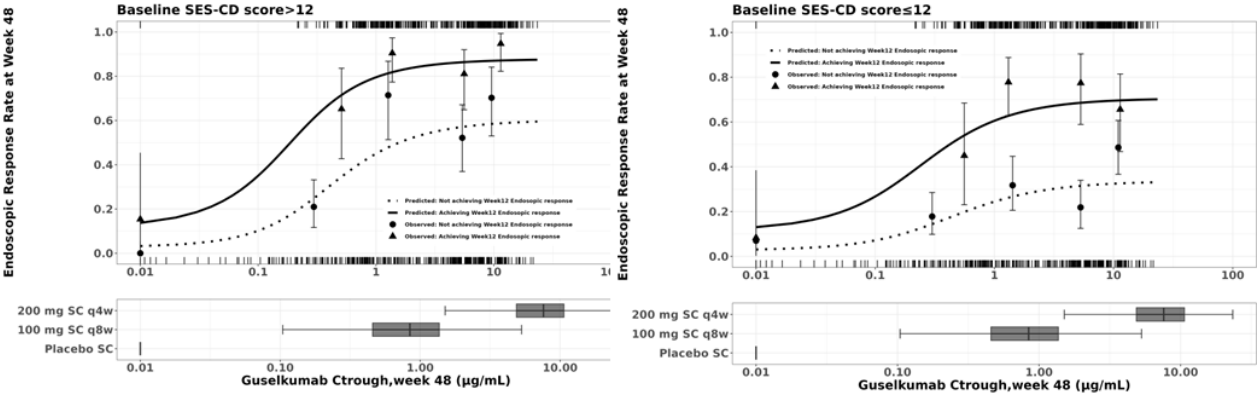


Figure 17: Model-predicted E-R Relationships for Endoscopic Response at Week 48 Using $C_{trough,\ week\ 48}$ as the PK Exposure Metric in Participants with CD, Stratified by Baseline SES-CD and Endoscopic Response at Week 12; Baseline SES-CD Score >12 (A) and Baseline SES-CD Score ≤12 (B)

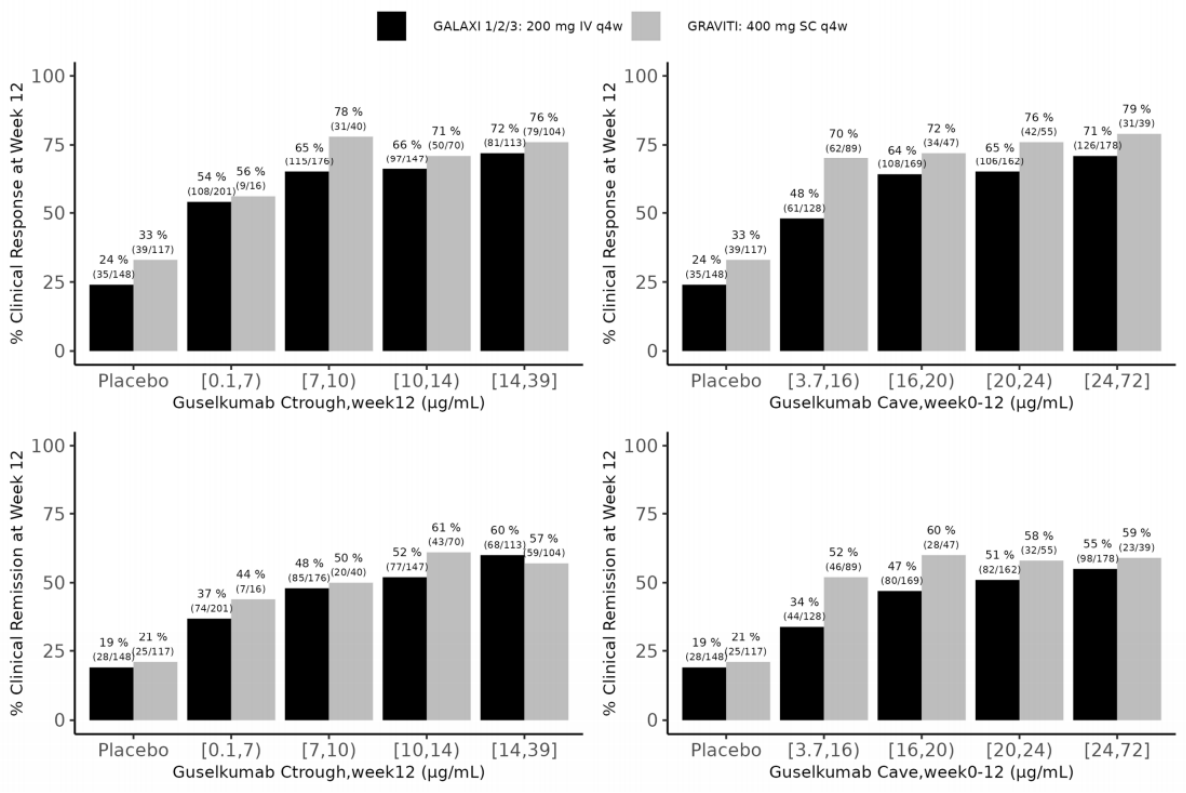


Exposure-response Comparison Between Intravenous and Subcutaneous Induction Treatments

The IV induction regimen (ie, 200 mg IV q4w) in the GALAXI studies and the SC induction regimen (ie, 400 mg SC q4w) in GRAVITI led to similar efficacy results at Weeks 12 and 24. To corroborate these findings, E-R graphical trends were compared between the IV induction regimen in the GALAXI studies and the SC induction regimen in GRAVITI (Figure 18).

In these analyses, guselkumab concentrations from the combined IV and SC induction treatment groups in the GALAXI studies and GRAVITI were divided into subgroups based on concentration quartiles at Week 12 (Ctrough, week12 and Cave, week0-12) and Week 24 (Ctrough, week24 and Cave, week0-24). In general, these results showed that comparable response rates were achieved following SC induction relative to IV induction in the same guselkumab concentration quartile subgroup for Week 12 efficacy endpoints (ie, clinical remission, clinical response, and endoscopic response) and for the Week 24 efficacy endpoint (ie, clinical remission).

Figure 18: Comparison of Exposure-response Trends (Left: Ctrough; Right: Cave) Between the Proposed IV Induction Treatment in GALAXI and the SC Induction Treatment in GRAVITI at Week 12



Exposure-response Analysis for Safety

Following induction treatment (200 mg IV q4w or 400 mg SC q4w) or maintenance treatment (100 mg SC q8w or 200 mg SC q4w) with guselkumab during the combined GALAXI studies or GRAVITI, no positive associations were observed between systemic guselkumab exposure and selected safety events (ie, infections, serious infections, SAEs) and liver function tests (ie, ALT, AST, total bilirubin).

Across the respective steady-state trough serum guselkumab concentration quartile subgroups during induction or maintenance, the ranges of the proportions of participants with safety events through Week 12, or from Week 12 through Week 24, were generally comparable between participants in GRAVITI and the combined GALAXI studies following IV induction treatment (200 mg IV q4w or 400 mg SC q4w) or SC maintenance treatment (100 mg SC q8w or 200 mg SC q4w).

2.3.5. Discussion on clinical pharmacology

Biopharmaceutics and bioanalytics

The assay to quantify guselkumab in plasma in patients with CD was the same as in patients with UC. The bioanalytic methods were assessed in procedure X/0043/G and found acceptable to the CHMP.

Pharmacokinetics in patients

Serum samples for the guselkumab assay were collected and analyzed in a Phase 2 dose-ranging study (GALAXI 1) and 3 Phase 3 studies (GALAXI 2 and 3, and GRAVITI). The effects of external and internal factors were investigated descriptively and using the POP-PK methodology. The results indicate that the pharmacokinetics of guselkumab are identical in the CD and UC patient groups. These results were also confirmed by the population pharmacokinetic analysis. In addition, similar covariates, such as

body weight, albumin, CRP, and prior biologic failure status, were found to influence the PK of guselkumab in both CD and UC conditions.

In the CD application, the dose proposed in the induction period was 400 mg SC. administered at 0, 4 and 8 weeks. This SC induction posology is based on the results of the GRAVITI study, for which data are available up to 24 weeks. Longer term efficacy data are available up to 48 weeks in the GALAXI studies where the induction was under the IV formulation. A comparison of the Ctrough at the end of the induction period indicates higher values following 400 mg SC administration compared to 200 mg IV administration, however, the difference disappears in a few weeks during the maintenance period. At 4 weeks of the maintenance period, the concentrations are independent of the dosage schedule in the induction period. The CHMP concludes that there is sufficient evidence to extrapolate the efficacy and safety data of the 48-week GALAXI studies to the 24-week GRAVITI study.

Pharmacodynamics

The PD response of guselkumab in relation to IL-17A, IL-22, and IFNγ, key effector cytokines associated with the IL-23 pathway, and CD was assessed by serum proteomics and RNA transcriptional profiling of ileal and colonic tissue. Considering the inflammatory biomarker efficacy results, the molecular analysis demonstrated that in evaluated subjects with CD, guselkumab reduced serum protein levels of IL-17A, IL-22 and IFNγ at Weeks 4 and Week 12 relative to pre-treatment levels and reduced colon mucosal biopsy RNA levels of IL-17A, IL-22 and IFNG at Week 12 relative to pre-treatment levels.

Immunogenicity

Treatment-emergent ADA incidence through Week 12 was 1.3%, ranging between 0% and 2.4% in the individual GALAXI studies. The presence of antibodies was not found to have an apparent impact on the PK or efficacy of guselkumab. The development of antibodies to guselkumab did not have an apparent impact on AEs within 1 hour of infusion or on injection site reactions. Immunogenicity results in patients with CD are included in SmPC Section 4.8.

PK/PD, Exposure – Response (E-R) relationships

Graphical analysis of the data showed that the clinical response at the end of the induction period moderately depends on Ctrough. The MAH assumes that the individual half-life, or induction period, is the predictor of the clinical effect measured at the end. However, the correlation disappears if the dose is also taken into account. Therefore, the MAH's hypothesis is unlikely. The role of Ctrough is also underlined by the results of the study GRAVITI. In this study, the measured Ctrough values were almost 50% higher, and accordingly, the clinical response ratio at the end of the induction period is consistently higher.

At the end of the maintenance period, the relationship between Ctrough and the therapeutic response is better described. At a higher Ctrough value, the effect no longer increases and the E-R curve reaches a plateau. Assuming that there is a well-defined relationship between Ctrough and clinical response, the MAH fitted the logistic model to the data. The logistic regression analysis of the predicted therapeutic responses shows that the logistic model describes reasonably well the clinical response dependence on concentration. In all cases except one, the observed response is within the confidence interval of the predicted response. However, for patients with a SES-CD score >12 who were not in endoscopic response at Week 12, the model was found to overestimate the expected endoscopic response rate.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology programme supports the use of guselkumab in the treatment of CD.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

CNTO1959CRD3001, Phase 2 study (GALAXI 1)

Methods

In the Phase 2 dose-ranging study, GALAXI 1, the guselkumab IV dose regimens spanned a wide induction dose range (200 mg IV, 600 mg IV, and 1200 mg IV) to support the induction dose regimens selected for confirmatory evaluation in Phase 3. The 12-week induction phase of the dose-ranging study GALAXI 1 was followed by a maintenance phase through Week 48. Participants who completed the 48-week Phase 2 GALAXI 1 study were eligible to enter the LTE to receive approximately 4 additional years of treatment, if the investigator considered that continued participation would benefit the participant.

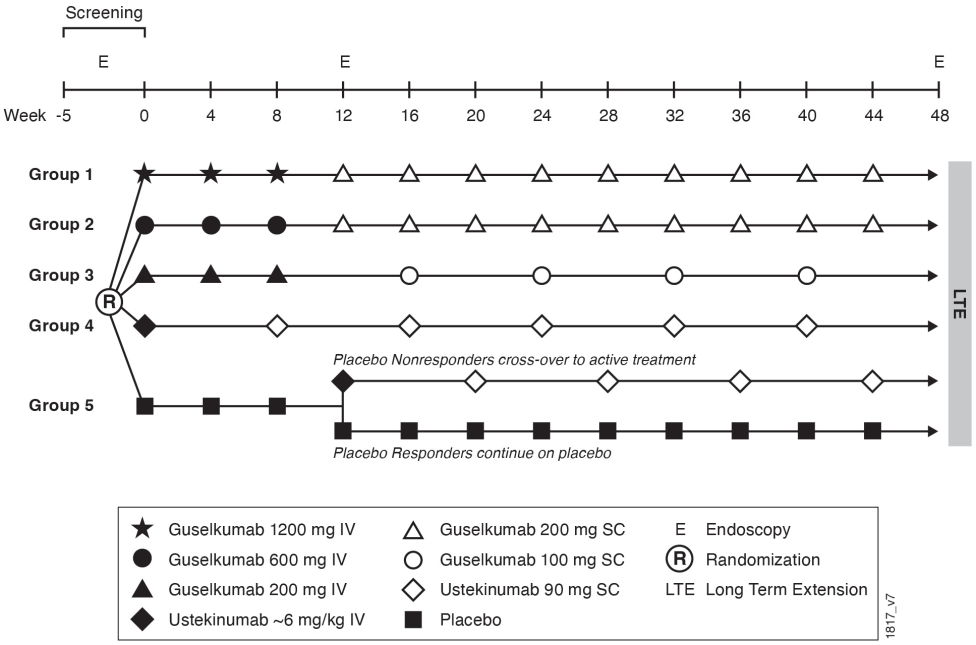
At Week 0, participants were randomized in a 1:1:1:1:1 ratio to receive the 1 of the following:

- Guselkumab Regimen 1: 1200 mg IV q4w ×3 → 200 mg SC q4w
- Guselkumab Regimen 2: 600 mg IV q4w ×3 → 200 mg SC q4w
- Guselkumab Regimen 3: 200 mg IV q4w ×3 → 100 mg SC q8w
- Ustekinumab: ~6 mg/kg IV → 90 mg SC q8w
- Placebo: Placebo IV q4w ×3 → Placebo SC q4w (for responders at Week 12) or ustekinumab crossover at Week 12 (for non-responders at Week 12)

An overview of the 5 treatment groups and their corresponding dosing schemes from Week 0 through Week 48 of the Phase 2 study is provided in Figure 19.

Participants were allocated to a treatment group using a permuted block randomization with baseline CDAI score (≤300 or >300) and prior biologic therapy failure or intolerance (BIO-Failure) status (Yes/No) as the stratification variables. Allocation to treatment group was performed using a central randomization center by means of an IWRS.

Figure 19: Study Schema: GALAXI 1 Dose Regimens from Week 0 to Week 48 in Phase 2 (CNTO1959CRD3001)



Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.

A prespecified Week 12 interim analysis (IA) was performed to inform Phase 3 induction dosing after the first 250 randomized participants completed Week 12 or terminated study participation before their Week 12 visit.

Participants continued to be randomized into the GALAXI 1 study while the prespecified Week 12 IA was ongoing. After the Phase 3 dose selection was made, no further participants were randomized into the GALAXI 1 Phase 2 study and randomization into the Phase 3 studies was initiated. All participants already randomized in the GALAXI 1 Phase 2 study continued in the study.

Treatment assignment blinding was maintained for investigative sites, site monitors, and participants until the Week 48 DBL for the GALAXI 1 study and analyses were completed.

In general, the Applicant remained blinded until the Week 48 DBL except for a limited number of Applicant's personnel who were unblinded at the time of the Week 12 IA and the Week 24 IA and they were not involved in study conduct. The Dose Selection Committee had access to the unblinded safety and efficacy summary level analyses, but the committee did not have access to individual participant treatment assignment, with the exception of a listing of SAEs, AEs leading to discontinuation of study intervention, and maximum postbaseline laboratory toxicity values for the purpose of safety evaluation. Both the Week 12 IA and the Week 24 IA were covered under an unblinding plan that limited the number of Applicant's personnel that had access to treatment assignment and/or summary level results.

The blind for the GALAXI 1 study was maintained with central readers for the endoscopy videos, as well as the central histology readers, being blinded to clinical outcomes, treatment assignments and study visits.

The GALAXI 1 study was unblinded after the Week 48 DBL and analyses were completed. Two CSRs are currently available: Week 48 CSR and Week 152 CSR.

Study participants

Since the dose-finding GALAXI 1 study was conducted under the same protocol as the two pivotal GALAXI 2 and GALAXI 3 studies, the inclusion and exclusion criteria were the same for the three GALAXI studies and they are presented in detail in Section 2.4.2. Main studies of this assessment report.

Objectives

Primary efficacy objective

- To evaluate the clinical efficacy of guselkumab in participants with CD

Secondary objectives

- To evaluate the dose-response of guselkumab
- To evaluate the efficacy of guselkumab on endoscopic improvement
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin

Other objectives

- To evaluate the impact of guselkumab on HRQOL and health economics outcome measures
- To evaluate the efficacy of guselkumab on histologic improvement
- To evaluate the impact of treatment with guselkumab on intestinal mucosal gene expressionprofiles and cellular composition associated with Crohn's disease

Outcomes/endpoints

Primary efficacy endpoint

- Change from baseline in the Crohns Disease Activity Index (CDAI) score at Week 12.

Major Secondary Endpoints

- Clinical remission at Week 12 (defined as CDAI score <150).
- Clinical response at Week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150).
- PRO-2 remission at Week 12 (defined as an AP mean daily score at or below 1 [AP≤1] AND a SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline).
- Clinical-biomarker response at Week 12 (clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin).
- Endoscopic response at Week 12 (defined as at least 50% improvement from baseline in the SES-CD or SES-CD score ≤2).

Long-term efficacy endpoints assessed from Week 12 through Week 48, without control for multiplicity:

- Clinical Remission
- Clinical Response
- CDAI
- Other PRO-2 Remission, AP, and SF
- Fistula Response

- Clinical-biomarker Endpoints and Inflammatory Biomarker Response Over Time
- Corticosteroid consumption
- BSFS
- AP-NRS
- PGIC/PGIS
- Endoscopic Endpoints
- Total GHAS/Histology
- HRQOL

Statistical methods

Analyses of the primary and major secondary endpoints were based on comparisons between each guselkumab treatment group and the placebo treatment group. The Type I error rate was controlled at the 0.05 (2 sided) significance level using a multiple testing procedure over the primary endpoint of change from baseline in the CDAI score at Week 12 and the major secondary endpoint of clinical remission at Week 12. Additional analyses of endpoints at other time points, including comparisons of guselkumab with ustekinumab at Week 48, were also performed.

Results

Demographics and Baseline Characteristics

Baseline demographic characteristics, baseline CD characteristics and CD-related medication history were generally similar across the treatment groups.

At baseline, 76.1% of participants were receiving 1 or more concomitant medications for CD. A total of 113 participants (36.6%) were receiving corticosteroids (including budesonide and beclomethasone dipropionate). The number of participants using corticosteroids (excluding budesonide and beclomethasone dipropionate) was lower in the 600 mg IV q4w → 200 mg SC q4w and 1200 mg IV q4w → 200 mg SC q4w groups (12 [19.0%] and 8 [13.1%] participants, respectively) compared with the 200 mg IV q4w → 100 mg SC q8w, ustekinumab, and placebo groups (18 [29.5%], 20 [31.7%], and 19 [31.1%] participants, respectively). The number of participants receiving budesonide was greater in the 1200 mg IV q4w → 200 mg SC q4w group (n=12 [19.7%]) compared with the 200 mg IV q4w → 100 mg SC q8w group (n=6 [9.8%]) and the 600 mg IV q4w → 200 mg SC q4w group (n=7 [11.1%]).

A total of 110 (35.6%) of participants were receiving immunomodulators (AZA, 6-MP, or MTX) at baseline. The proportions of participants using immunomodulators were lower in the 200 mg IV → 100 mg SC q8w and 600 mg IV → 200 mg SC q8w groups (24.6% and 28.6%, respectively) compared with the 1200 mg IV→ 200 mg SC q4w, ustekinumab, and placebo groups (41.0%, 41.3%, and 42.6%, respectively).

The majority of participants were white (84.5%) and male (59.2%). The median age was 36 years (range 18 to 76 years). The mean duration of CD was 8.8 years, the median CDAI score was 297, the median SES-CD score was 11.0, the median fecal calprotectin level was 610.0 mg/kg, and the median CRP concentration was 5.7 mg/L.

A total of 168 (54.4%) participants had a history of biologic failure (BIO-Failure) and 141 (45.6%) had failed conventional therapies but not biologic therapy (CON-Failure); the majority of the CON-Failure participants (n=112) were BIO-Naïve.

At baseline, 76.1% of participants were receiving 1 or more concomitant medications for CD, including corticosteroids (36.6%), and immunomodulators (AZA, 6-MP, or MTX; 35.6%).

Discontinuation of Study Intervention

Nine (2.9%) participants in the Primary Efficacy Analysis Set discontinued study intervention prior to Week 12. Forty-two (13.6%) participants discontinued study intervention between Week 0 and Week 48. There were no obvious differences among the treatment groups in participants who discontinued study intervention before Week 12.

Efficacy Results

Week 12 (induction phase)

Results on primary endpoint and key endpoints at Week 12 are provided in Table 14 and Table 15 respectively.

Table 14: Primary endpoint (CDAI scores) at Week 12, GALAXI 1, Primary efficacy analysis set

		Guselkumab				
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w	Combined	Ustekinumab[a]
Analysis set: Primary efficacy analysis set	61	61	63	61	185	63
Baseline						
N	61	61	63	61	185	63
Mean (SD)	300.8 (49.91)	304.6 (57.24)	305.8 (58.77)	305.8 (54.46)	305.4 (56.57)	313.3 (61.30)
Median	296.0	300.0	299.0	293.0	299.0	298.0
IQ range	(267.0; 333.0)	(258.0; 348.0)	(254.0; 347.0)	(257.0; 340.0)	(257.0; 345.0)	(264.0; 361.0)
Range	(231; 417)	(215; 447)	(226; 434)	(236; 431)	(215; 447)	(222; 448)
Week 12 [b,c]						
N	60	60	62	58	180	63
Mean (SD)	266.3 (105.92)	143.4 (98.57)	164.8 (104.88)	160.0 (83.78)	156.1 (96.29)	175.6 (105.06)
Median	283.0	120.0	137.0	157.0	139.5	156.0
IQ range	(189.5; 340.5)	(77.0; 218.0)	(99.0; 227.0)	(93.0; 217.0)	(91.0; 226.0)	(83.0; 261.0)
Range	(20; 474)	(-30; 363)	(-22; 455)	(6; 341)	(-30; 455)	(20; 435)
Change from baseline Week 12 [b,c]						
N	60	60	62	58	180	63
Mean (SD)	-34.4 (104.85)	-159.8 (110.52)	-139.2 (100.71)	-143.7 (96.58)	-147.5 (102.62)	-137.7 (96.12)
Median	-16.0	-165.0	-146.0	-159.5	-155.0	-135.0
IQ range	(-102.0; 27.5)	(-230.0; -90.0)	(-205.0; -65.0)	(-210.0; -59.0)	(-216.0; -68.5)	(-207.0; -59.0)
Range	(-249; 174)	(-402; 35)	(-321; 93)	(-354; 66)	(-402; 93)	(-321; 30)
LS Mean (SE) [d]	-36.2 (12.39)	-160.4 (12.38)	-138.9 (12.19)	-144.9 (12.62)	-148.0 (7.16)	-135.9 (12.18)
LS Mean Difference (95% CI)[d] from Placebo		124.2 (89.8, 158.7)	102.7 (68.5, 136.9)	108.7 (73.9, 143.5)	111.8 (83.7, 140.0)	
p-value [d]		< 0.001	< 0.001	< 0.001	< 0.001	

[a]Subjects received a single ustekinumab IV induction dose (~6 mg/kg IV) at Week 0. At Week 8, subjects received one ustekinumab SC maintenance dose (90 mg SC).
[b]Subjects who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease-related surgery, or discontinued study agent due to lack of efficacy or an AE of worsening Crohn's disease prior to Week 12 had their baseline value carried forward. Subjects who had discontinued study agent due to any other reasons prior to Week 12 had their observed Week 12 data used, if available.
[c]Subjects who had insufficient data to calculate the CDAI score at Week 12 did not have their missing data imputed.
[d]The LS Mean and SE for each treatment group, LS Mean difference between the treatment groups and p-values for the comparisons of each guselkumab treatment group with the placebo group were based on MMRM analysis including change from baseline in CDAI as the response; treatment group, visit, baseline CDAI score, BIO-Failure status (yes, no), an interaction term of visit with treatment group and an interaction term of visit with baseline CDAI score as explanatory variables.

Table 15: Key Endpoints at Week 12 in CNTO1959CRD3001 Phase 2 Study (GALAXI 1); Primary Efficacy Analysis Set

		Guselkumab		
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w
Primary Efficacy Analysis Set	61	61	63	61
CDAI change from baseline, N	60	60	62	58
LS mean (SE)[b]	-36.2 (12.39)	-160.4 (12.38)	-138.9 (12.19)	-144.9 (12.62)
LS mean[b] difference (95% CI) from placebo		124.2 (89.8, 158.7)	102.7 (68.5, 136.9)	108.7 (73.9, 143.5)
p-value[b]		< 0.001	< 0.001	< 0.001
N	61	61	63	61
Subjects in clinical remission[c]	10 (16.4%)	35 (57.4%)	35 (55.6%)	28 (45.9%)
Adjusted treatment difference (95% CI)[d]		41.2 (25.9, 56.4)	40.2 (25.5, 54.9)	30.4 (15.2, 45.5)
p-value[e]		< 0.001	< 0.001	< 0.001
N	61	61	63	61
Subjects in clinical response[f]	15 (24.6%)	43 (70.5%)	42 (66.7%)	37 (60.7%)
Adjusted treatment difference (95% CI)[d]		46.0 (30.4, 61.6)	42.6 (27.0, 58.2)	37.0 (21.3, 52.6)
p-value*[e]		< 0.001	< 0.001	< 0.001
N	61	61	63	61
Subjects in PRO-2 remission[g]	10 (16.4%)	27 (44.3%)	32 (50.8%)	20 (32.8%)
Adjusted treatment difference (95% CI)[d]		28.1 (12.6, 43.6)	34.6 (19.6, 49.5)	16.9 (2.3, 31.6)
p-value*[e]		< 0.001	< 0.001	0.031
N	61	61	63	61
Subjects in clinical-biomarker response[h]	4 (6.6%)	33 (54.1%)	31 (49.2%)	23 (37.7%)
Adjusted treatment difference (95% CI)[d]		48.5 (35.0, 62.1)	42.4 (28.8, 56.0)	31.8 (18.3, 45.3)
p-value*[e]		< 0.001	< 0.001	< 0.001
N	61	61	63	61
Subjects in endoscopic response[i]	7 (11.5%)	23 (37.7%)	23 (36.5%)	20 (32.8%)
Adjusted treatment difference (95% CI)[d]		26.2 (11.5, 40.9)	24.5 (10.1, 38.8)	22.6 (8.4, 36.8)
p-value*[j]		0.001	0.002	0.003
N	61	61	63	61
Subjects in endoscopic remission[k]	2 (3.3%)	10 (16.4%)	7 (11.1%)	10 (16.4%)
Adjusted treatment difference (95% CI)[d]		12.1 (2.2, 22.1)	7.5 (-1.5, 16.4)	13.3 (2.9, 23.8)
p-value*[j]		0.027	0.114	0.015

* This endpoint was not controlled for multiplicity; nominal p-values are presented.

a: Subjects received a single ustekinumab IV induction dose at Week 0. At Week 8, subjects received one ustekinumab SC maintenance dose (90 mg SC).

b: The LS Mean (SE) for each treatment group, LS Mean difference (CI) between the treatment groups and the p-values for the comparisons of each guselkumab treatment group with the placebo group were based on MMRM analysis including change from baseline in CDAI as the response; treatment group, visit, baseline CDAI score, BIO-Failure status (yes, no), an interaction term of visit with treatment group and an interaction term of visit with baseline CDAI score as explanatory variables.

c: Clinical remission is defined as CDAI score <150.

d: Confidence intervals were based on the Wald statistic with Mantel-Haenszel weight for pairwise comparisons of each guselkumab treatment group with the placebo treatment group.

e: p-Values for pairwise comparisons of each guselkumab treatment group with the placebo treatment group were based on CMH chi-square test stratified by baseline CDAI score (≤300 or >300) and BIO-Failure status (yes or no).

f: Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150.

G: PRO-2 remission is defined as the unweighted CDAI component of daily average abdominal pain (AP) score ≤1 AND the unweighted CDAI component of daily average stool frequency (SF) score ≤3, and no worsening of AP or SF from baseline.

h: Clinical-biomarker response is defined as clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin.

i: Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2.

j: p-Values for pairwise comparisons of each guselkumab treatment group with the placebo treatment group were based on CMH chi-square test stratified by baseline SES-CD score (≤12 or >12) and BIO-Failure status (yes or no).

k: Endoscopic remission is defined as SES-CD score ≤2.

Week 48 (maintenance phase)

At Week 48, the reference comparison group for the endpoints was the ustekinumab group. The GALAXI 1 study was not powered for comparisons at Week 48.

Results on the key clinical efficacy endpoints at Week 48 are included in Table 16.

Table 16: Key Endpoints at Week 48 in CNTO1959CRD3001 Phase 2 Study (GALAXI 1); Primary Efficacy Analysis Set

	Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	600 mg IV q4w → 200 mg SC q4w	1200 mg IV q4w → 200 mg SC q4w	Ustekinumab[a]
Primary Efficacy Analysis Set	61	63	61	63
CDAI change from baseline, N	56	59	51	59
LS mean (SE)[b]	-195.5 (12.38)	-204.4 (12.13)	-190.8 (12.86)	-161.7 (12.12)
N	61	63	61	63
Subjects in clinical remission [c]	39 (63.9%)	46 (73.0%)	35 (57.4%)	37 (58.7%)
N	61	63	61	63
Subjects in durable clinical remission [d]	31 (50.8%)	39 (61.9%)	25 (41.0%)	30 (47.6%)
N	61	63	61	63
Subjects in corticosteroid-free clinical remission [e]	36 (59.0%)	45 (71.4%)	34 (55.7%)	37 (58.7%)
N	61	63	61	63
Subjects in PRO-2 remission [f]	35 (57.4%)	44 (69.8%)	31 (50.8%)	29 (46.0%)
N	61	63	61	63
Subjects in endoscopic response [g]	27 (44.3%)	29 (46.0%)	27 (44.3%)	19 (30.2%)
N	61	63	61	63
Subjects in endoscopic remission [h]	11 (18.0%)	11 (17.5%)	20 (32.8%)	4 (6.3%)

a: Subjects received a single ustekinumab IV induction dose (~6 mg/kg IV) at Week 0. At Week 8, subjects received one ustekinumab SC maintenance dose (90 mg SC).
b: The LS Mean and SE for each treatment group, for the comparisons of each guselkumab treatment group with the ustekinumab group were based on MMRM analysis including change from baseline in CDAI as the response; treatment group, visit, baseline CDAI score, BIO-Failure status (yes, no), an interaction term of visit with treatment group and an interaction term of visit with baseline CDAI score as explanatory variables.
c: Clinical remission is defined as CDAI score <150.
d: Durable clinical remission is defined as CDAI score <150 for ≥80% of all visits between Week 12 and Week 48 (ie, at least 8 of 10 visits), which must include Week 48.
e: Corticosteroid-free clinical remission is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
f: PRO-2 remission is defined as the unweighted CDAI component of daily average abdominal pain (AP) score ≤1 AND the unweighted CDAI component of daily average stool frequency (SF) ≤ 3, and no worsening of AP or SF from baseline.
g: Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2.
h: Endoscopic remission is defined as SES-CD score ≤2.

Phase 3 Dose Selection

A prespecified Week 12 IA in GALAXI 1 was performed to inform Phase 3 induction dosing after the first 250 randomized participants completed Week 12 or terminated study participation before their Week 12 visit. The selected induction and maintenance dose regimens for Phase 3 were:

- 200 mg IV q4w ×3 → 200 mg SC q4w
- 200 mg IV q4w ×3 → 100 mg SC q8w

The results of the Week 12 IA showed no clear evidence of an IV induction dose-response across all key efficacy endpoints of change in CDAI, clinical response, clinical remission, endoscopic response and change in SES-CD. At Week 12, in participants treated with guselkumab, there was no apparent association between serum guselkumab concentration and improvement in the CDAI score or in the proportions of participants achieving clinical remission. Therefore, the 200 mg IV induction dose was selected for evaluation in the Phase 3 studies.

Two maintenance doses were selected for evaluation after induction: 1) a high maintenance dose of 200 mg SC q4w was selected to maximize the potential to achieve and maintain efficacy by sustaining exposures only slightly lower than the exposures achieved during induction; and 2) a dose of 100 mg SC q8w, which is the approved dose for psoriasis and psoriatic arthritis was selected to evaluate whether efficacy is maintained with lower exposures than used during induction. These dosing regimens were intended to allow further characterization of the dose/exposure-response relationship of guselkumab maintenance treatment in Phase 3.

Week 152

The GALAXI 1 study continued with an LTE and the Week 152 clinical study report (CSR) reported efficacy through Week 144, safety through Week 152, and real-life patient handling data through the timepoint of the DBL.

A total of 360 participants were randomized and treated in the randomized, double-blind period of the main study (GALAXI 1 Week 48). Of the 360 participants, 252 participants were treated in the LTE period. A total of 21.0% (53/252) of participants discontinued study intervention from Week 48 through Week 152.

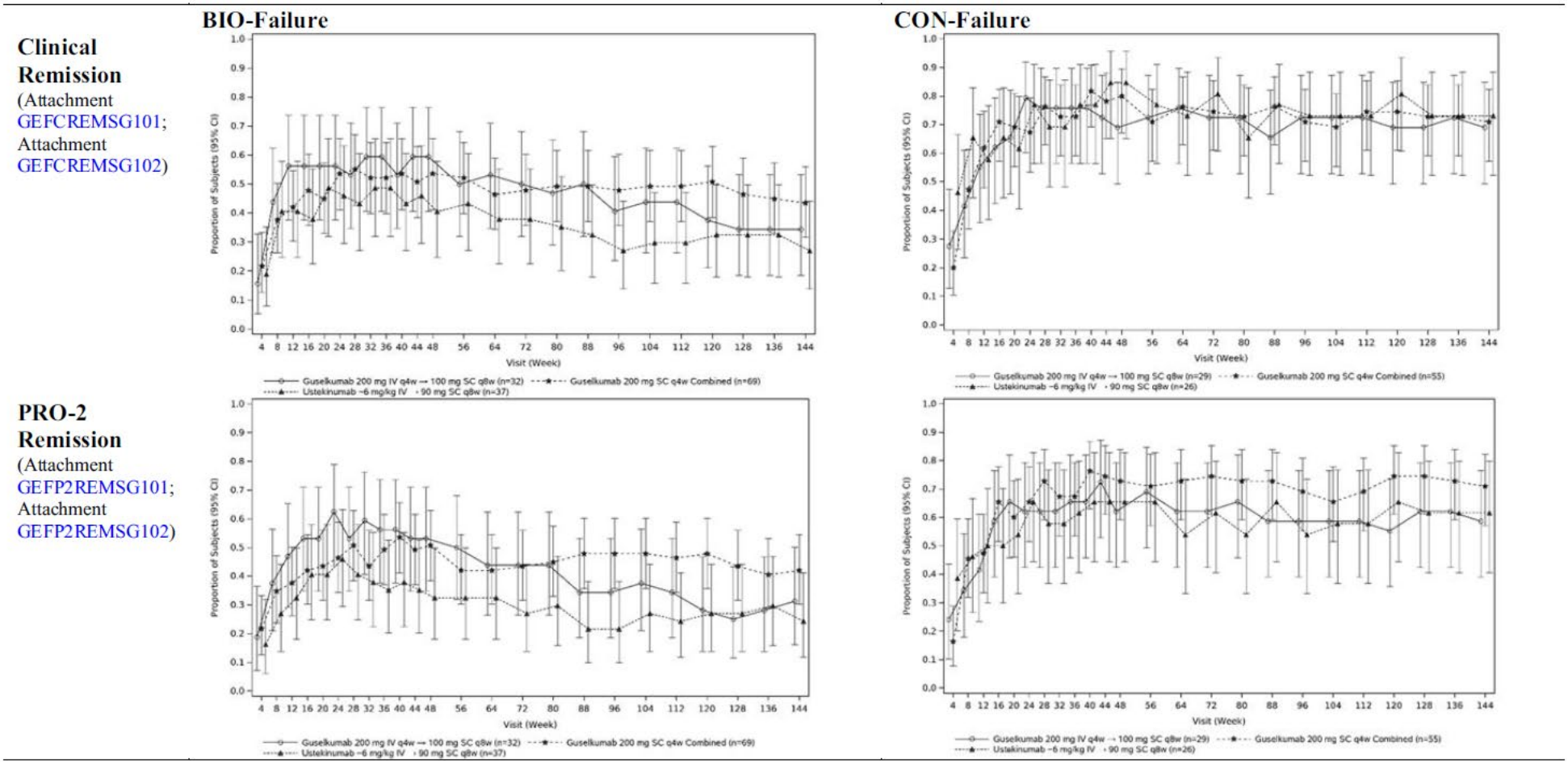
When describing the GALAXI 1 Week 152 results, the following guselkumab arms are used for the Primary Efficacy Analysis Set:

- Guselkumab combined 200 mg SC q4w (600 mg IV q4w → 200 mg SC q4w and 1200 mg IV q4w → 200 mg SC q4w)
- Guselkumab 100 mg SC q8w treatment group (200 mg IV q4w → 100 mg SC q8w)

The results presented hereafter are based on PAS. Participants who did not enter LTE are also included and were considered as non-responder after Week 48.

A similar trend through Week 144 was also observed for PRO-2 remission. At Week 144, 54.8% in the guselkumab combined 200 mg SC q4w treatment group, 44.3% in the guselkumab 100 mg SC q8w treatment group, and 39.7% in the randomized ustekinumab treatment group achieved PRO-2 remission.

Figure 20: Proportion of participants by clinical remission and PRO-2 remission by visit from Week 4 through Week 144 based on over time supplementary estimand 1, primary efficacy analysis analysis set



2.4.2. Main studies

2.4.2.1. Study CNTO1959CRD3001 – GALAXI 2 and GALAXI 3

GALAXI 2 and GALAXI 3 studies were conducted under the single protocol CNTO1959CRD3001.

Methods

Study participants

Main inclusion criteria

This study enrolled participants at least 18 years of age at the time of informed consent and diagnosed with moderately to severely active CD (of at least 3 months' duration).

At baseline, participants must have met the following key target disease criteria:

- Clinically active CD (baseline CDAI score ≥220 but ≤450 and either mean daily stool frequency count >3 or mean daily AP score >1).
- Endoscopic evidence of ileocolonic CD (screening SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease), based on the presence of ulceration in any 1 of the 5 ileocolonic segments.
- Population eligible for systemic therapy:
    - participants who demonstrated an inadequate response or failed to tolerate:
        - previous conventional therapy (CON-Failure) (ie, oral corticosteroids or immunomodulators [6-MP/AZA/MTX]) OR
        - biologic therapy (BIO-Failure) (ie, TNF antagonists or vedolizumab).
        - BIO-Naïve (ie, naïve to biologic therapy such as TNF antagonist or vedolizumab or ustekinumab) patients
        - BIO-nonfailure patients (i.e. exposed to biologic therapy but had not demonstrated inadequate response or tolerance)

Main exclusion criteria

- Participants must not have had complications of CD as specified in the protocol (eg. complications requiring surgery, or precluding the use of the CDAI, abscess, stoma – non-exhaustive list)
- Participants with prior exposure to IL-12/23 or IL-23 agents were ineligible for study entry, with the exception of participants who have had limited exposure to and who had not demonstrated failure or intolerance to ustekinumab.
- Infection-related exclusion criteria, including active TB

Treatments

The 4 treatment groups and their corresponding dose regimens from Week 0 through Week 48 in the Phase 3 studies GALAXI 2 and GALAXI 3 were as follows:

Participants remained on their assigned treatment regimens for the 48-week study, except for the placebo group as outlined below.

- Guselkumab Regimen 1 (200 mg IV q4w ×3 → 200 mg SC q4w)

Guselkumab 200 mg IV induction q4w: Weeks 0, 4, and 8 (ie, total of 3 IV doses); at Week 12, continued treatment with guselkumab 200 mg SC maintenance q4w through Week 44.

- Guselkumab Regimen 2 (200 mg IV q4w ×3 → 100 mg SC q8w)

Guselkumab 200 mg IV induction q4w: Weeks 0, 4, and 8 (ie, total of 3 IV doses); at Week 16, continued treatment with guselkumab 100 mg SC maintenance q8w through Week 40.

- Active Control – Ustekinumab (~6 mg/kg IV → 90 mg SC q8w)

A single ustekinumab IV induction dose at Week 0 (weight-based IV dose approximating 6 mg/kg as outlined below); at Week 8, ustekinumab SC maintenance (90 mg SC q8w) through Week 40.

    - Ustekinumab 260 mg (weight ≤55 kg)
    - Ustekinumab 390 mg (weight >55 kg and ≤85 kg)
    - Ustekinumab 520 mg (weight >85 kg)

- Placebo → Placebo or Ustekinumab Crossover

Placebo IV q4w: Weeks 0, 4, and 8 (ie, total of 3 IV doses); at Week 12, continued treatment based on clinical response status, as follows:

    - Placebo responders: Continued placebo SC q4w treatment from Week 12 through Week 44.
    - Placebo non-responders: Single ustekinumab IV induction dose at Week 12 (weight-based IV doses approximating 6 mg/kg as outlined above); at Week 20, continued ustekinumab SC maintenance (90 mg SC q8w) through Week 44.

Concomitant medication:

Participants receiving oral 5-ASA compounds, oral corticosteroids, conventional immunomodulators (ie, AZA, 6-MP, or MTX), antibiotics, and/or enteral nutrition for the treatment of CD at baseline maintained a stable dose for the specified period before baseline.

In general, participants receiving these medications for CD at baseline (ie, Week 0) of all 3 studies maintained a stable dose through Week 48, with the exception of oral corticosteroids. Therapies could be discontinued or reduced in dose after Week 0 if investigator judgment required it because of toxicity or other medical necessity; even if the toxicity resolved, the therapy was not be restarted. Corticosteroids were maintained at baseline doses through Week 12, and all participants began tapering corticosteroids at Week 12, unless medically not feasible.

From Week 0 through Week 48 of each study, enrolled participants did not initiate any of the following concomitant CD-specific medical therapies:

- Oral or rectal 5-ASA compounds.
- Immunomodulators (ie, AZA, 6-MP, or MTX).

- Oral, parenteral, or rectal corticosteroids, including budesonide and beclomethasone dipropionate.
- Antibiotics as a primary treatment for CD.
- Total parenteral nutrition or enteral nutrition as a treatment for CD.

If the above medical therapies were initiated or medication doses increased based on medical necessity (i.e. worsening of CD) as assessed by the investigator, participants continued to attend all study visits and had all assessments. While this did not represent a deviation from the study protocol and the participants could remain on their assigned therapy (guselkumab, ustekinumab, or placebo), it was considered a treatment failure.

During the treatment phase of LTE (ie, Week 48 through Week 240), concomitant therapies for CD including 5-ASAs, corticosteroids, antibiotics, and immunomodulators (ie, AZA, 6-MP, or MTX), and/or total parenteral or enteral nutrition could be administered and changed at the discretion of the investigator.

No treatment/dose adjustment was permitted through Week 48. After that time point, treatment adjustment for inadequate response is permitted between Week 52 and Week 80.

Objectives

Primary Objectives

- To evaluate the clinical and endoscopic efficacy of guselkumab in participants with CD
- To evaluate the safety of guselkumab

Secondary Objectives

- To evaluate the impact of guselkumab on HRQOL
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin

Outcomes/endpoints

Co-primary endpoints

- Clinical remission at Week 12
- Endoscopic response at Week 12

Since GALAXI 2 and GALAXI 3 had 2 different guselkumab treatment arms with the same induction dose (200 mg IV q4w ×3 → 200 mg SC q4w and 200 mg IV q4w ×3 → 100 mg SC q8w), the data from both guselkumab treatment arms within each study are combined for induction comparisons to placebo at Week 12 and referred to as the combined guselkumab IV treatment group (200 mg IV induction dose).

Major secondary endpoints

The major secondary endpoints included 3 sets of comparisons:

- Short-term endpoints at Week 12 evaluating guselkumab compared with placebo:
    - PRO-2 remission at Week 12

- fatigue response at Week 12
- endoscopic remission (Region-specific definition) at Week 12

- Long-term endpoints at Week 48 evaluating guselkumab compared with placebo:
  - corticosteroid-free clinical remission at Week 48
  - endoscopic response at Week 48
- Long-term endpoints at Week 48 evaluating guselkumab compared with ustekinumab:
  - endoscopic remission (Region-specific definition) at Week 48
  - clinical remission at Week 48
  - endoscopic response at Week 48
  - durable clinical remission at Week 48
  - PRO-2 remission at Week 48
  - clinical remission at Week 48 and endoscopic response at Week 48
  - corticosteroid-free clinical remission at Week 48

Table 17: Definitions of Endpoints (CNTO1959CRD3001 GALAXI 2)

Endpoint	Definition
Clinical response	≥100-point reduction from baseline in CDAI score or CDAI score <150
Clinical remission	CDAI <150
Endoscopic response	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
Corticosteroid-free clinical remission at Week 48	CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48
Fatigue response	An improvement of ≥7 points in PROMIS Fatigue Short Form 7a
Durable clinical remission	CDAI <150 for ≥80% of all visits between Week 12 and Week 48 [ie, at least 8 of 10 visits]), which must include Week 48
PRO-2 remission	AP mean daily score at or below 1 [AP≤1] and SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline
Endoscopic remission (Region-specific definition)	SES-CD score ≤2
Deep remission (Region-specific definition)	Clinical remission and endoscopic remission (Region-specific definition)

Sample size

The power for the key endpoints, as well as the number of participants necessary to assess the safety of guselkumab in the GALAXI 2 and GALAXI 3 studies, were considered in determining the sample size. Based on this, a total sample size of approximately 490 participants per study, consisting of 140 participants in each of the 2 guselkumab treatment groups, 70 participants in the placebo treatment group, and 140 participants in the ustekinumab treatment group were to provide at least 90% power for the co-primary endpoints (egion-specific) in each study based on a chi-square test at the 0.05 (2-sided) significance level.

Randomisation

At Week 0, participants were randomly allocated to GALAXI 2 or GALAXI 3, using a permuted block randomization with baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), prior BIO-Failure status (Yes/No), and baseline corticosteroid use (Yes/No) as stratification variables. Within each stratum, participants in each study were randomized in a 2:2:2:1 ratio to receive 1 of 2 dose regimens of guselkumab, ustekinumab, or placebo, respectively. Allocation to treatment groups was performed using a central randomization center by means of an IWRS.

Blinding (masking)

The Applicant remained blinded to the GALAXI 2 and GALAXI 3 treatment assignments until after the Week 48 DBL for GALAXI 2 and GALAXI 3 occurred. The investigators and participants remained blinded until after the Week 48 DBL occurred and analyses were completed.

The central readers for the endoscopy videos, as well as the central histology readers, were blinded to clinical outcomes, treatment assignments and study visits.

The GALAXI studies applied a double-dummy approach such that all active intervention infusions or injections had a matching placebo administration, including the ustekinumab crossover.

Statistical methods

Efficacy Analysis sets

Table 18: Efficacy Analysis Sets (CNTO1959CRD3001 GALAXI 2 and 3)

Efficacy Analysis Sets	Description
PAS	All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria[a]
ATAS	All randomized participants who received at least 1 (partial or complete) dose of study intervention.
Modified PAS	Same as the PAS but excludes participants who have data that could not be verified as specified by the Global Monitoring Plan due to the inability to access sites because of a major disruption (specifically, the regional crisis in Ukraine and Russia, or COVID-related site restrictions such as site closures, and other potential events that restrict site access).
Week 12 Treated PAS	All randomized participants who received study intervention at Week 12 and satisfied the SES-CD eligibility criteria[a].

Region-specific co-primary endpoints:

- Clinical remission at Week12
- Endoscopic response at Week12

Co-primary estimands:

- Estimand 1R: Clinical remission at Week12. A binary response variable (response/nonresponse) where response was defined as a CDAI score <150 at Week12, without experiencing any of the ICEs in categories 1-3 and 5 as outlined below prior to the Week 12 visit.
- Estimand 2R: Endoscopic response at Week12. A binary response variable (response/nonresponse) where response was defined as a ≥50% improvement from baseline in

SES-CD score or SES-CD ≤2 at Week12, without experiencing any of the ICEs in categories 1-3 and 5 as outlined below prior to the Week 12 visit.

The Region-specific co-primary estimands were defined by 5 attributes: study intervention, population, variable (endpoint), ICEs and corresponding strategies, and population-level summary.

The following intercurrent events were defined:

ICE Identifier	ICE Description	Corresponding Strategy
1	A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.)	Composite
2	A prohibited change in CD medication	Composite
3	Discontinuation of study intervention due to 1) lack of efficacy, or 2) an AE of worsening of CD	Composite
4	Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis.	Treatment Policy
5	Discontinuation of study intervention for reasons other than those specified in ICEs 3 and 4.	Composite

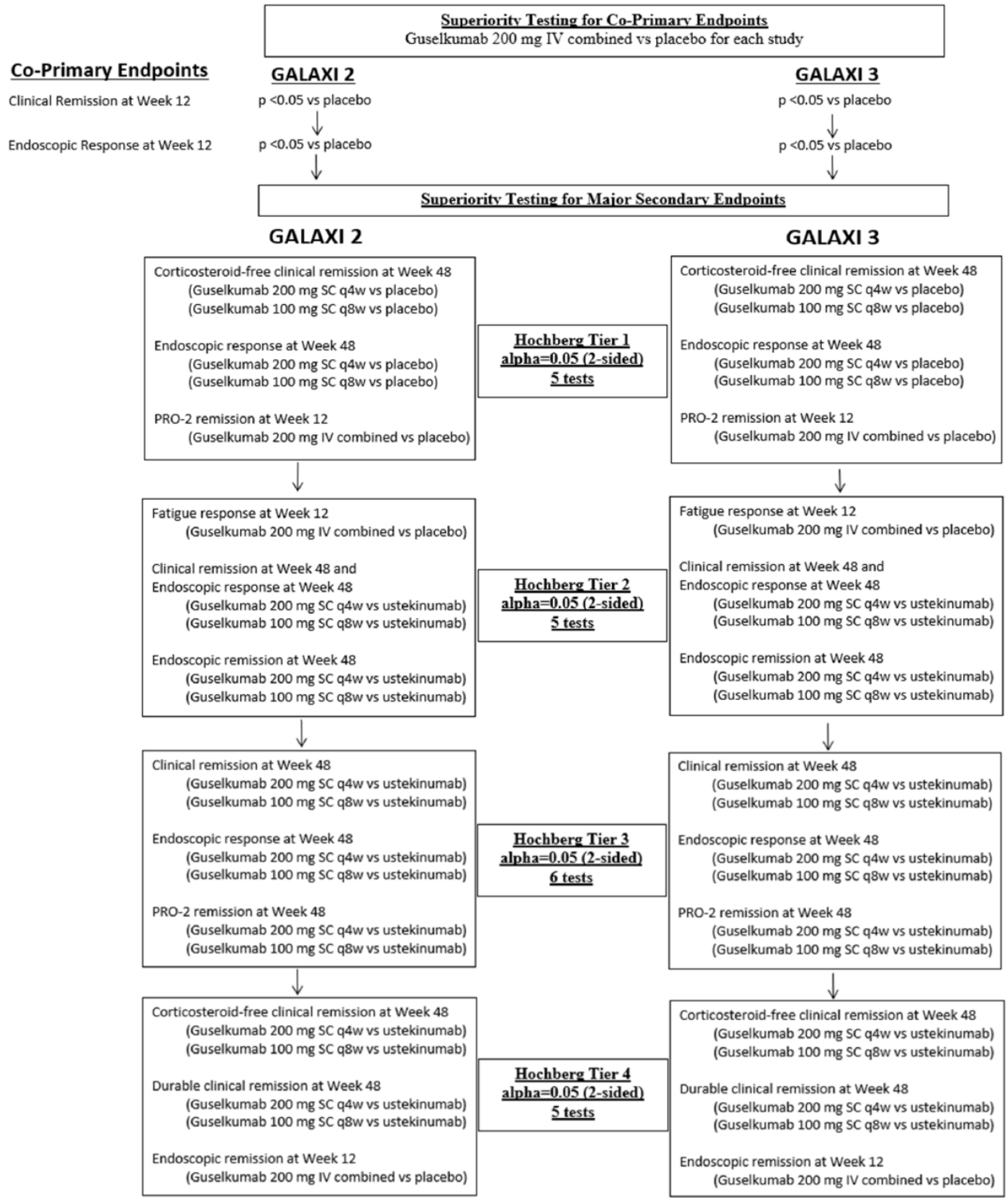
The difference in proportions of responders (according to the variable 1R or 2R defined above) between the guselkumab induction dose group (guselkumab 200 mg IV) and the placebo treatment group was assessed. The analyses of the co-primary estimands were based on the PAS.

Regarding the ICE strategies, for the treatment policy strategy, the associated ICE event was ignored, and any data observed after the associated ICE event were used for the analysis. After accounting for the ICE strategies, any missing data were handled by the missing data rules.

For the co-primary endpoint related to clinical remission, if the CDAI score could not be calculated at Week12, the CDAI score was considered missing at Week12. For the co-primary endpoint of endoscopic response at Week 12, the SES-CD score was calculated based on the main approach.

The Type 1 error rate was controlled across the co-primary and major secondary endpoints. The testing procedure began with sequential tests of superiority of the combined guselkumab dose group compared with placebo relative to the co-primary endpoints at the 2-sided 0.05 significance level. After testing of the co-primary endpoints, and if all p-values were significant (ie, $p < 0.05$), the testing procedure continued with superiority tests for the major secondary endpoints, which were grouped into 4 tiers (Figure 21).

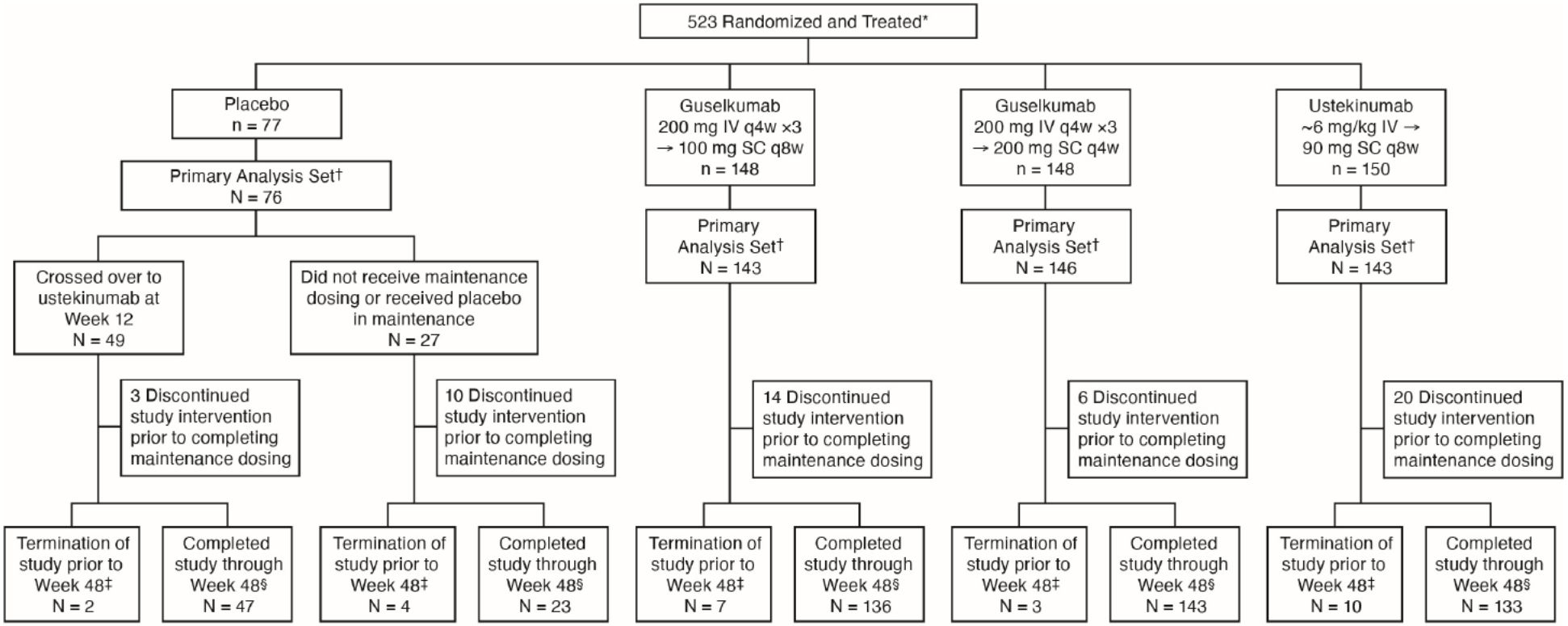
Figure 21: Region-specific testing procedure (CNT01959CRD3001 GALAXI 3) Separate testing procedure for GALAXI 2 and GALAXI 3)



Results

Participant flow

Figure 22: Disposition of All Randomized Participants Through Week 48 in CNTO1959CRD3001 (GALAXI 2)



* 1 participant was randomized but not treated.

† The primary analysis set includes the 508 participants who were randomized and received at least 1 dose of study intervention (including a partial dose) and satisfied the SES-CD eligibility criteria eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).

‡ End of Study Disposition = 'Terminated' and study day is prior to Day 343.

§ Continued into LTE or completed Final Efficacy and Safety (FES) Visit prior to Week 48.

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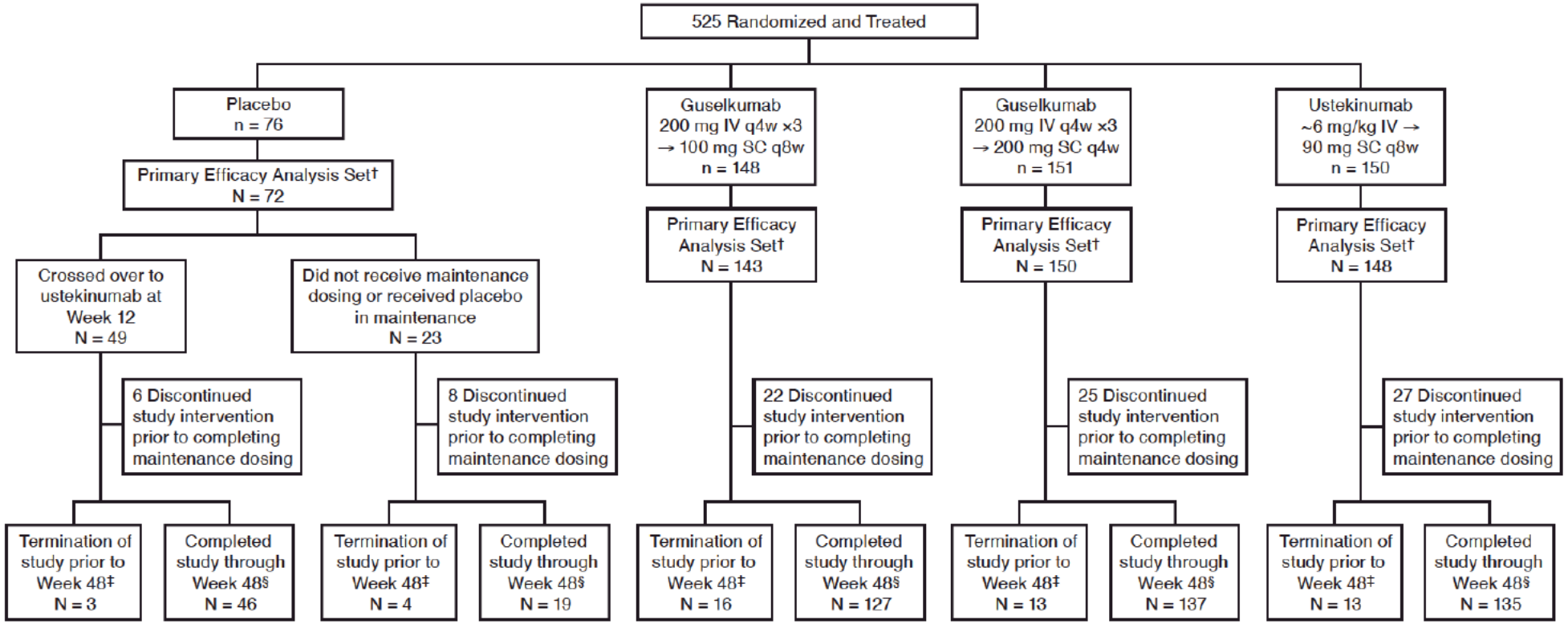
Figure 23: Disposition of All Randomized Participants Through Week 48 in CNTO1959CRD3001 (GALAXI 3)



† The primary efficacy analysis set includes the 513 participants who were randomized and received at least 1 dose of study intervention (including a partial dose) and satisfied the SES-CD eligibility criteria eligibility criteria adopted in Protocol Amendment 3 (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).

‡ End of Study Disposition = 'Terminated' and study day is prior to Day 343.

§ Continued into LTE or completed Final Efficacy and Safety (FES) Visit prior to Week 48.

4848_v9

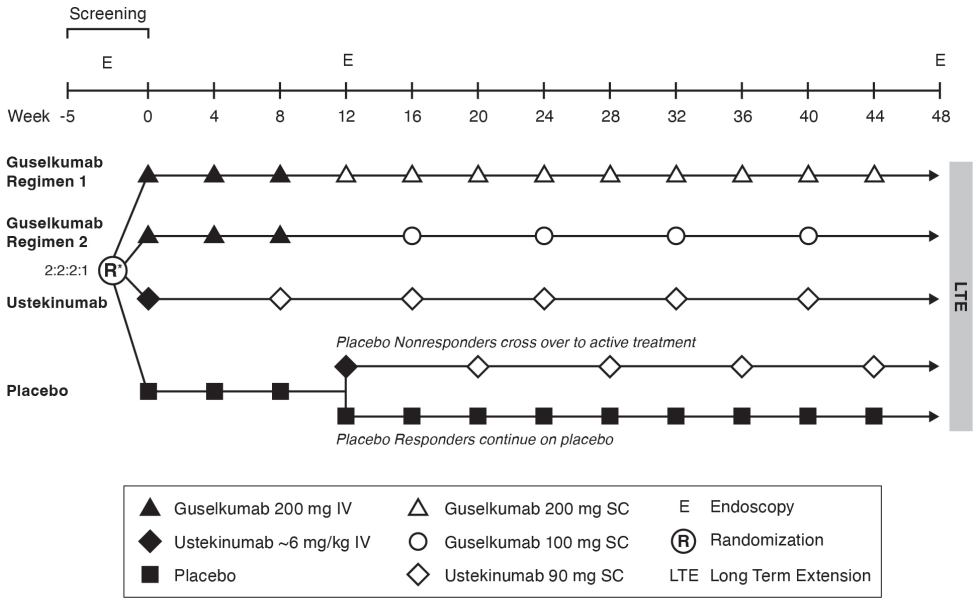
Recruitment

Initiation date of GALAXI 2: 8 January 2020. Data Cutoff Date: 20 October 2023. The study is ongoing.

Initiation date of GALAXI 3: 22 January 2020. Data Cutoff Date: 16 October 2023. The study is ongoing.

Conduct of the study

Figure 24: Conduct of studies GALAXI 2 and 3



Note: This schematic only illustrates the dosing for the treatment groups. It does not provide a complete illustration of all blinding (placebo) administrations.

* Randomization stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No).

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Protocol amendments

Two protocol amendments considered substantial occurred before the start of GALAXI 2 and 3:

Amendment 1 (10 December 2018): to revise the endoscopic inclusion criterion, which was changed to enroll study participants with evidence of ulceration in any 1 of the 5 ileocolonic segments. Additional clarifications throughout the protocol were based on feedback from health authorities, ethics committees, and investigative sites.

Amendment 2 (13 November 2019): to specify the guselkumab induction and maintenance doses to be administered in the Phase 3 studies (GALAXI 2 and GALAXI 3) based on the Week 12 IA from GALAXI 1. Clarifying information about the management of liver function test abnormalities. Of note, after the Week 12 IA to inform induction and maintenance dose selection for the Phase 3 studies, an urgent safety measure due to an event of toxic hepatitis in a participant in the guselkumab 1200 mg IV treatment group resulted in a temporary pause of induction dosing, effective 24 October 2019.

Three protocol amendments were considered substantial occurred after the start of GALAXI 2:

Amendment 3 (20 October 2020): to add a real-life patient handling substudy to collect data about new 2 mL devices in the GALAXI 1 LTE.

SES-CD inclusion criteria were revised from an SES-CD ≥3 to an SES-CD ≥6 (or ≥4 for participants with isolated ileal disease). Endoscopic response at Week 12 was added as a co-primary endpoint. These changes were made based on Health Authority feedback and Phase 2 (GALAXI 1) results.

Amendment 4 (21 July 2021): to extend the duration of the LTE from 2 years to 4 years for all participants in the GALAXI studies.

Amendment 5 (12 July 2022) to the GALAXI 2 and GALAXI 3 studies: Modification of the co-primary endpoints resulted in separate Global (for FDA approval) and Region-specific (for EU approval) co-primary endpoints. Major secondary endpoints were also adjusted. Decrease of the sample size in the GALAXI Phase 3 studies from 1540 participants to approximately 980 participants (approximately 490 participants in each Phase 3 study). Measures taken regarding any event of Major Disruption, including the COVID 19 pandemic, war, or natural disaster.

Protocol deviations

Table 19: Subjects with Major Protocol Deviations through Week 48, primary analysis set – GALAXI 2 study

			Guselkumab				
	Placebo[a]	Placebo → Ustekinumab[b]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	76	49	143	146	289	143	508
Subjects with major protocol deviations	8 (10.5%)	3 (6.1%)	29 (20.3%)	21 (14.4%)	50 (17.3%)	28 (19.6%)	89 (17.5%)
Entered but did not satisfy criteria	4 (5.3%)	0	9 (6.3%)	6 (4.1%)	15 (5.2%)	6 (4.2%)	25 (4.9%)
Received wrong treatment or incorrect dose	0	0	3 (2.1%)	2 (1.4%)	5 (1.7%)	1 (0.7%)	6 (1.2%)
Received wrong treatment or incorrect dose - regional crisis related	0	0	0	0	0	0	0
Developed withdrawal criteria but not withdrawn	0	0	0	0	0	0	0
Received a disallowed concomitant treatment	0	0	0	0	0	0	0
Other	6 (7.9%)	3 (6.1%)	18 (12.6%)	14 (9.6%)	32 (11.1%)	22 (15.4%)	63 (12.4%)
Other – COVID-19	0	0	0	0	0	0	0
Other – regional crisis related	1 (1.3%)	3 (6.1%)	2 (1.4%)	2 (1.4%)	4 (1.4%)	0	8 (1.6%)

Table 20: Summary of Subjects With Major Protocol Deviations of "Other" Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

			Guselkumab				
	Placebo [a]	Placebo → UST [b]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	UST ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	76	50	143	146	289	143	508
Subjects with major protocol deviations classified as 'other'	6 (7.9%)	3 (6.0%)	18 (12.6%)	14 (9.6%)	32 (11.1%)	22 (15.4%)	63 (12.4%)
Other	6 (7.9%)	3 (6.0%)	18 (12.6%)	14 (9.6%)	32 (11.1%)	22 (15.4%)	63 (12.4%)
Clinical laboratory assessments not taken for two or more consecutive visits	3 (3.9%)	3 (6.0%)	4 (2.8%)	9 (6.2%)	13 (4.5%)	7 (4.9%)	26 (5.1%)
Deviations from approved IPPI process	0	0	9 (6.3%)	4 (2.7%)	13 (4.5%)	6 (4.2%)	19 (3.7%)
Video ileocolonoscopy not performed at W12 and/or W48	0	0	3 (2.1%)	1 (0.7%)	4 (1.4%)	2 (1.4%)	6 (1.2%)
Consented with incorrect initial main ICF	0	0	0	0	0	5 (3.5%)	5 (1.0%)
CRP or calpro done at local lab 2 consecutive visits	0	0	1 (0.7%)	1 (0.7%)	2 (0.7%)	1 (0.7%)	3 (0.6%)
Accidental unblinding of treatment group of a subject or a blinded staff member	1 (1.3%)	0	1 (0.7%)	0	1 (0.3%)	0	2 (0.4%)
CDAI calculated in error at W0 or W12 which impact clinical response	2 (2.6%)	0	0	0	0	0	2 (0.4%)
Non-delegated personnel performed study-related assessment or procedures	0	0	0	0	0	2 (1.4%)	2 (0.4%)
Re-consent not done	0	0	1 (0.7%)	0	1 (0.3%)	1 (0.7%)	2 (0.4%)
Missed two consecutive visits due to reasons other than AE or SAE	0	0	0	0	0	1 (0.7%)	1 (0.2%)
Other - regional crisis related	1 (1.3%)	3 (6.0%)	2 (1.4%)	2 (1.4%)	4 (1.4%)	0	8 (1.6%)
Clinical laboratory assessments not taken for two or more consecutive visits	1 (1.3%)	3 (6.0%)	2 (1.4%)	2 (1.4%)	4 (1.4%)	0	8 (1.6%)

UST=ustekinumab.

[a] Protocol deviations in this column are attributed to those subjects randomized to placebo with one exception: in the case where a subject is randomized to placebo and crosses over to ustekinumab, protocol deviations occurring after receiving ustekinumab are not counted in this column.

[b] Subjects who are placebo nonresponders and crossed over to ustekinumab at Week 12. Protocol deviations counted in this group occurred after the subject switched to the ustekinumab treatment group.

Note: Subjects may appear in more than one category. Deviations from the sections "Other - COVID-related" and "Other - regional crisis related" are also included in "Other" section.

Table 21: Subjects with Major Protocol Deviations through Week 48, primary analysis set – GALAXI 3 study

			Guselkumab				
	Placebo[a]	Placebo → Ustekinumab[b]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	49	143	150	293	148	513
Subjects with major protocol deviations	14 (19.4%)	2 (4.1%)	27 (18.9%)	36 (24.0%)	63 (21.5%)	40 (27.0%)	119 (23.2%)
Entered but did not satisfy criteria	7 (9.7%)	0	9 (6.3%)	18 (12.0%)	27 (9.2%)	19 (12.8%)	53 (10.3%)
Received wrong treatment or incorrect dose	0	0	4 (2.8%)	3 (2.0%)	7 (2.4%)	2 (1.4%)	9 (1.8%)
Received wrong treatment or incorrect dose - regional crisis related	0	0	1 (0.7%)	0	1 (0.3%)	0	1 (0.2%)
Developed withdrawal criteria but not withdrawn	0	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.2%)
Received a disallowed concomitant treatment	0	0	0	0	0	0	0
Other	7 (9.7%)	2 (4.1%)	16 (11.2%)	20 (13.3%)	36 (12.3%)	25 (16.9%)	70 (13.6%)
Other – COVID-19	0	0	1 (0.7%)	0	1 (0.3%)	2 (1.4%)	3 (0.6%)
Other – regional crisis related	0	1 (2.0%)	1 (0.7%)	3 (2.0%)	4 (1.4%)	1 (0.7%)	6 (1.2%)

Table 22: Summary of Subjects With Major Protocol Deviations of "Other" Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

			Guselkumab				
	Placebo [a]	Placebo → UST [b]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	UST ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	49	143	150	293	148	513
Subjects with major protocol deviations classified as 'other'	7 (9.7%)	2 (4.1%)	16 (11.2%)	20 (13.3%)	36 (12.3%)	25 (16.9%)	70 (13.6%)
Other	7 (9.7%)	2 (4.1%)	16 (11.2%)	20 (13.3%)	36 (12.3%)	25 (16.9%)	70 (13.6%)
Clinical laboratory assessments not taken for two or more consecutive visits	2 (2.8%)	2 (4.1%)	8 (5.6%)	8 (5.3%)	16 (5.5%)	15 (10.1%)	35 (6.8%)
Deviations from approved IPPI process	3 (4.2%)	0	7 (4.9%)	8 (5.3%)	15 (5.1%)	4 (2.7%)	22 (4.3%)
Consented with incorrect initial main ICF	0	0	0	1 (0.7%)	1 (0.3%)	3 (2.0%)	4 (0.8%)
Video ileocolonoscopy not performed at W12 and/or W48	0	0	0	1 (0.7%)	1 (0.3%)	3 (2.0%)	4 (0.8%)
Accidental unblinding of treatment group of a subject or a blinded staff member	1 (1.4%)	0	2 (1.4%)	0	2 (0.7%)	0	3 (0.6%)
Administration of IP deemed unacceptable for use	0	0	0	1 (0.7%)	1 (0.3%)	1 (0.7%)	2 (0.4%)
CDAI calculated in error at W0 or W12 which impact clinical response	0	0	1 (0.7%)	0	1 (0.3%)	1 (0.7%)	2 (0.4%)
Missed two consecutive visits due to reasons other than AE or SAE	1 (1.4%)	0	0	1 (0.7%)	1 (0.3%)	0	2 (0.4%)
Deviation from IP process for preparation and administration	0	0	0	0	0	1 (0.7%)	1 (0.2%)
Non-delegated personnel performed study related assessment or procedures	0	0	0	0	0	1 (0.7%)	1 (0.2%)
Re-consent not done	0	0	0	1 (0.7%)	1 (0.3%)	0	1 (0.2%)
Other - COVID-19	0	0	1 (0.7%)	0	1 (0.3%)	2 (1.4%)	3 (0.6%)
Clinical laboratory assessments not taken for two or more consecutive visits	0	0	1 (0.7%)	0	1 (0.3%)	1 (0.7%)	2 (0.4%)
Video ileocolonoscopy not performed at W12 and/or W48	0	0	0	0	0	1 (0.7%)	1 (0.2%)

			Guselkumab				
	Placebo [a]	Placebo → UST [b]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	UST ~6 mg/kg IV → 90 mg SC q8w	Total
Other - regional crisis related	0	1 (2.0%)	1 (0.7%)	3 (2.0%)	4 (1.4%)	1 (0.7%)	6 (1.2%)
Clinical laboratory assessments not taken for two or more consecutive visits	0	1 (2.0%)	1 (0.7%)	3 (2.0%)	4 (1.4%)	1 (0.7%)	6 (1.2%)

UST=ustekinumab.
[a] Protocol deviations in this column are attributed to those subjects randomized to placebo with one exception: in the case where a subject is randomized to placebo and crosses over to ustekinumab, protocol deviations occurring after receiving ustekinumab are not counted in this column.
[b] Subjects who are placebo nonresponders and crossed over to ustekinumab at Week 12. Protocol deviations counted in this group occurred after the subject switched to the ustekinumab treatment group.
Note: Subjects may appear in more than one category. Deviations from the sections "Other - COVID-related" and "Other - regional crisis related" are also included in "Other" section.

Baseline data

Demography

Table 23: Summary of Demographics and Baseline Characteristics; Primary Analysis Set (GALAXI 2)

		Guselkumab			Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined		
Analysis set: Primary	76	143	146	289	143	508
Age, years						
N	76	143	146	289	143	508
Mean (SD)	34.2 (11.86)	37.2 (12.92)	36.1 (13.09)	36.7 (12.99)	36.9 (12.70)	36.4 (12.76)
Median	32.0	34.0	33.5	34.0	36.0	34.0
Range	(18; 67)	(19; 83)	(18; 69)	(18; 83)	(18; 74)	(18; 83)
IQ range	(25.0; 39.5)	(28.0; 46.0)	(26.0; 44.0)	(26.0; 46.0)	(26.0; 45.0)	(26.0; 44.0)
Sex						
N	76	143	146	289	143	508
Female	35 (46.1%)	74 (51.7%)	59 (40.4%)	133 (46.0%)	59 (41.3%)	227 (44.7%)
Male	41 (53.9%)	69 (48.3%)	87 (59.6%)	156 (54.0%)	84 (58.7%)	281 (55.3%)
Race						
N	76	143	146	289	143	508
American Indian or Alaska Native	0	0	0	0	0	0
Asian	17 (22.4%)	34 (23.8%)	28 (19.2%)	62 (21.5%)	32 (22.4%)	111 (21.9%)
Black or African American	0	3 (2.1%)	1 (0.7%)	4 (1.4%)	3 (2.1%)	7 (1.4%)
Native Hawaiian or Other Pacific Islander	2 (2.6%)	0	0	0	0	2 (0.4%)
White	55 (72.4%)	103 (72.0%)	115 (78.8%)	218 (75.4%)	104 (72.7%)	377 (74.2%)
Multiple	0	0	0	0	0	0
Not Reported	2 (2.6%)	3 (2.1%)	2 (1.4%)	5 (1.7%)	4 (2.8%)	11 (2.2%)
Ethnicity						
N	76	143	146	289	143	508
Hispanic or Latino	2 (2.6%)	4 (2.8%)	8 (5.5%)	12 (4.2%)	5 (3.5%)	19 (3.7%)
Not Hispanic or Latino	70 (92.1%)	135 (94.4%)	134 (91.8%)	269 (93.1%)	132 (92.3%)	471 (92.7%)
Not Reported	4 (5.3%)	4 (2.8%)	4 (2.7%)	8 (2.8%)	6 (4.2%)	18 (3.5%)
Region						
N	76	143	146	289	143	508
Asia	17 (22.4%)	33 (23.1%)	28 (19.2%)	61 (21.1%)	31 (21.7%)	109 (21.5%)
Eastern Europe	37 (48.7%)	68 (47.6%)	72 (49.3%)	140 (48.4%)	69 (48.3%)	246 (48.4%)
North America	3 (3.9%)	11 (7.7%)	8 (5.5%)	19 (6.6%)	12 (8.4%)	34 (6.7%)
Rest of world	19 (25.0%)	31 (21.7%)	38 (26.0%)	69 (23.9%)	31 (21.7%)	119 (23.4%)
Weight, kg						

N	76	143	146	289	143	508
Mean (SD)	64.51 (15.319)	66.61 (15.647)	67.23 (15.442)	66.93 (15.520)	67.93 (16.745)	66.85 (15.850)
Median	62.05	64.40	65.00	65.00	65.90	65.00
Range	(36.3; 108.2)	(41.0; 113.6)	(38.8; 114.9)	(38.8; 114.9)	(36.5; 126.0)	(36.3; 126.0)
IQ range	(54.10; 74.55)	(54.50; 77.70)	(56.50; 76.40)	(55.90; 76.70)	(55.20; 78.10)	(55.10; 77.00)
Height, cm						
N	76	143	146	289	143	508
Mean (SD)	170.11 (9.750)	169.38 (10.041)	170.60 (9.480)	170.00 (9.764)	170.79 (10.179)	170.24 (9.867)
Median	170.00	169.00	171.00	170.00	170.00	170.00
Range	(150.0; 194.0)	(150.0; 193.0)	(144.8; 198.1)	(144.8; 198.1)	(148.0; 191.0)	(144.8; 198.1)
IQ range	(163.50; 178.25)	(162.00; 176.10)	(164.00; 178.00)	(163.00; 177.00)	(163.00; 180.00)	(163.00; 178.00)
Body mass index, kg/m^2						
N	76	143	146	289	143	508
Mean (SD)	22.21 (4.517)	23.10 (4.596)	23.01 (4.544)	23.06 (4.562)	23.19 (4.958)	22.97 (4.672)
Median	21.88	22.23	22.40	22.34	22.56	22.32
Range	(12.7; 33.3)	(15.0; 39.6)	(13.9; 37.7)	(13.9; 39.6)	(14.4; 42.6)	(12.7; 42.6)
IQ range	(18.45; 24.97)	(20.06; 25.61)	(19.55; 26.05)	(19.69; 25.64)	(19.33; 25.76)	(19.48; 25.57)

Key: SD=standard deviation, IQ=interquartile
a Placebo column includes all subjects randomized to placebo. At Week 12, subjects who were clinical responders continued placebo treatment and those who were
nonresponders crossed over to ustekinumab.
Note: N's for each parameter reflect non-missing values.

Table 24: Summary of Demographics and Baseline Characteristics; Primary Analysis Set (GALAXI 3)

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	143	150	293	148	513
Age, years						
N	72	143	150	293	148	513
Mean (SD)	35.4 (12.52)	34.9 (11.44)	37.6 (13.44)	36.3 (12.56)	37.9 (13.69)	36.6 (12.89)
Median	33.0	33.0	35.0	33.0	35.0	34.0
Range	(18; 69)	(18; 68)	(18; 72)	(18; 72)	(18; 76)	(18; 76)
IQ range	(24.5; 43.0)	(26.0; 43.0)	(27.0; 47.0)	(27.0; 43.0)	(27.0; 46.0)	(26.0; 44.0)
Sex						
N	72	143	150	293	148	513
Female	25 (34.7%)	58 (40.6%)	59 (39.3%)	117 (39.9%)	64 (43.2%)	206 (40.2%)
Male	47 (65.3%)	85 (59.4%)	91 (60.7%)	176 (60.1%)	84 (56.8%)	307 (59.8%)
Race						
N	72	143	150	293	148	513
American Indian or Alaska Native	0	0	0	0	0	0
Asian	18 (25.0%)	38 (26.6%)	28 (18.7%)	66 (22.5%)	22 (14.9%)	106 (20.7%)
Black or African American	3 (4.2%)	0	1 (0.7%)	1 (0.3%)	4 (2.7%)	8 (1.6%)
Native Hawaiian or Other Pacific Islander	2 (2.8%)	1 (0.7%)	0	1 (0.3%)	1 (0.7%)	4 (0.8%)
White	47 (65.3%)	103 (72.0%)	117 (78.0%)	220 (75.1%)	115 (77.7%)	382 (74.5%)
Multiple	0	0	0	0	0	0
Not Reported	2 (2.8%)	1 (0.7%)	4 (2.7%)	5 (1.7%)	6 (4.1%)	13 (2.5%)
Ethnicity						
N	72	143	150	293	148	513
Hispanic or Latino	4 (5.6%)	7 (4.9%)	5 (3.3%)	12 (4.1%)	11 (7.4%)	27 (5.3%)
Not Hispanic or Latino	67 (93.1%)	132 (92.3%)	141 (94.0%)	273 (93.2%)	129 (87.2%)	469 (91.4%)
Not Reported	1 (1.4%)	4 (2.8%)	4 (2.7%)	8 (2.7%)	8 (5.4%)	17 (3.3%)
Region						
N	72	143	150	293	148	513
Asia	18 (25.0%)	36 (25.2%)	28 (18.7%)	64 (21.8%)	22 (14.9%)	104 (20.3%)
Eastern Europe	34 (47.2%)	63 (44.1%)	66 (44.0%)	129 (44.0%)	63 (42.6%)	226 (44.1%)
North America	7 (9.7%)	12 (8.4%)	12 (8.0%)	24 (8.2%)	20 (13.5%)	51 (9.9%)
Rest of world	13 (18.1%)	32 (22.4%)	44 (29.3%)	76 (25.9%)	43 (29.1%)	132 (25.7%)

Baseline demographics were similar across the treatment groups in the BIO-Failure, CON-Failure, and BIO-Naive subgroups.

Table 25: CD related baseline disease characteristics – GALAXI 2 study

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	76	143	146	289	143	508
Crohn's disease duration (years)						
N	76	143	146	289	143	508
Mean (SD)	6.36 (7.484)	7.91 (7.232)	7.30 (6.696)	7.60 (6.961)	6.58 (6.505)	7.13 (6.926)
Median	4.06	5.98	4.69	5.69	4.56	4.92
Range	(0.2; 46.6)	(0.3; 38.3)	(0.3; 29.9)	(0.3; 38.3)	(0.3; 26.7)	(0.2; 46.6)
IQ range	(1.57; 7.65)	(1.83; 11.34)	(2.50; 10.81)	(2.27; 11.15)	(1.57; 8.28)	(1.86; 10.18)
≤ 5 years	44 (57.9%)	56 (39.2%)	79 (54.1%)	135 (46.7%)	78 (54.5%)	257 (50.6%)
>5 and ≤ 15 years	24 (31.6%)	65 (45.5%)	47 (32.2%)	112 (38.8%)	48 (33.6%)	184 (36.2%)
>15 years	8 (10.5%)	22 (15.4%)	20 (13.7%)	42 (14.5%)	17 (11.9%)	67 (13.2%)
CDAI Score						
N	76	143	146	289	143	508
Mean (SD)	292.0 (51.70)	297.3 (52.57)	294.2 (51.69)	295.7 (52.06)	295.3 (52.35)	295.0 (52.00)
Median	283.5	287.0	283.5	285.0	283.0	284.5
Range	(220; 430)	(220; 439)	(221; 442)	(220; 442)	(221; 443)	(220; 443)
IQ range	(252.5; 320.0)	(253.0; 334.0)	(252.0; 330.0)	(252.0; 332.0)	(259.0; 329.0)	(254.0; 330.0)
Stool frequency count > 3	56 (73.7%)	108 (75.5%)	100 (68.5%)	208 (72.0%)	108 (75.5%)	372 (73.2%)
Abdominal pain score > 1	71 (93.4%)	136 (95.1%)	140 (95.9%)	276 (95.5%)	133 (93.0%)	480 (94.5%)
Stool frequency count > 3 and Abdominal pain score > 1	51 (67.1%)	101 (70.6%)	94 (64.4%)	195 (67.5%)	98 (68.5%)	344 (67.7%)
SES-CD						
N	76	143	146	289	143	508
Mean (SD)	13.9 (7.80)	13.0 (7.03)	12.4 (7.14)	12.7 (7.07)	13.3 (7.50)	13.1 (7.31)
Median	11.0	11.0	11.0	11.0	11.0	11.0
Range	(5; 37)	(4; 36)	(4; 39)	(4; 39)	(4; 44)	(4; 44)
IQ range	(8.0; 19.0)	(7.0; 17.0)	(7.0; 17.0)	(7.0; 17.0)	(7.0; 18.0)	(7.0; 18.0)
Endoscopic disease severity per SES-CD score						
N	76	143	146	289	143	508
< 7	14 (18.4%)	21 (14.7%)	29 (19.9%)	50 (17.3%)	26 (18.2%)	90 (17.7%)
7-16	38 (50.0%)	83 (58.0%)	79 (54.1%)	162 (56.1%)	75 (52.4%)	275 (54.1%)
> 16	24 (31.6%)	39 (27.3%)	38 (26.0%)	77 (26.6%)	42 (29.4%)	143 (28.1%)
CRP concentration (mg/L)						
N	76	143	146	289	143	508
Mean (SD)	13.4 (21.84)	13.8 (19.94)	14.7 (20.47)	14.3 (20.18)	13.8 (17.78)	14.0 (19.76)
Median	4.6	7.1	5.9	6.4	7.5	6.1
Range	(0; 147)	(0; 127)	(0; 108)	(0; 127)	(0; 125)	(0; 147)
IQ range	(1.7; 15.8)	(1.9; 17.1)	(2.1; 17.1)	(2.1; 17.1)	(2.8; 17.8)	(2.2; 16.9)
≤ 3	27 (35.5%)	43 (30.1%)	47 (32.2%)	90 (31.1%)	38 (26.6%)	155 (30.5%)
> 3	49 (64.5%)	100 (69.9%)	99 (67.8%)	199 (68.9%)	105 (73.4%)	353 (69.5%)
Fecal calprotectin (µg/g)						
N	76	142	145	287	138	501
Mean (SD)	1802.9 (2050.60)	1929.2 (3752.84)	1510.1 (1998.86)	1717.4 (2999.86)	1671.1 (2144.17)	1717.6 (2653.24)
Median	961.0	856.0	962.0	934.0	1003.0	966.0
Range	(15; 8302)	(15; 36000)	(15; 15804)	(15; 36000)	(15; 13602)	(15; 36000)
IQ range	(257.5; 2763.5)	(388.0; 1751.0)	(272.0; 1790.0)	(349.0; 1790.0)	(351.0; 1852.0)	(344.0; 1921.0)
≤ 250	19 (25.0%)	23 (16.2%)	34 (23.4%)	57 (19.9%)	24 (17.4%)	100 (20.0%)
> 250	57 (75.0%)	119 (83.8%)	111 (76.6%)	230 (80.1%)	114 (82.6%)	401 (80.0%)
Fecal calprotectin >250 µg/g and CRP >3 mg/L						
N	76	142	145	287	138	501
Yes	42 (55.3%)	88 (62.0%)	83 (57.2%)	171 (59.6%)	91 (65.9%)	304 (60.7%)
No	34 (44.7%)	54 (38.0%)	62 (42.8%)	116 (40.4%)	47 (34.1%)	197 (39.3%)
IBDQ						
N	75	142	143	285	140	500
Mean (SD)	126.9 (30.19)	123.8 (33.17)	128.0 (30.07)	125.9 (31.67)	127.5 (30.54)	126.5 (31.09)
Median	128.0	124.0	125.0	124.0	126.0	126.0
Range	(47; 197)	(46; 205)	(56; 202)	(46; 205)	(49; 213)	(46; 213)
IQ range	(104.0; 143.0)	(103.0; 145.0)	(106.0; 146.0)	(105.0; 145.0)	(107.5; 147.0)	(105.0; 145.0)
Involved GI areas (assessed by central reader)						
N	76	143	146	289	143	508
Ileum only	17 (22.4%)	29 (20.3%)	39 (26.7%)	68 (23.5%)	25 (17.5%)	110 (21.7%)
Colon only	29 (38.2%)	62 (43.4%)	56 (38.4%)	118 (40.8%)	58 (40.6%)	205 (40.4%)
Ileum and Colon	30 (39.5%)	52 (36.4%)	51 (34.9%)	103 (35.6%)	60 (42.0%)	193 (38.0%)

Number of subjects with at least 1 open or draining fistula	7 (9.2%)	21 (14.7%)	7 (4.8%)	28 (9.7%)	9 (6.3%)	44 (8.7%)
1 fistula	5 (6.6%)	18 (12.6%)	5 (3.4%)	23 (8.0%)	6 (4.2%)	34 (6.7%)
>1 fistulas	2 (2.6%)	3 (2.1%)	2 (1.4%)	5 (1.7%)	3 (2.1%)	10 (2.0%)
Number of subjects with at least 1 open or draining fistula	7	21	7	28	9	44
Median	1.0	1.0	1.0	1.0	1.0	1.0
Range	(1; 3)	(1; 3)	(1; 3)	(1; 3)	(1; 3)	(1; 3)
Perianal	7 (100.0%)	21 (100.0%)	6 (85.7%)	27 (96.4%)	7 (77.8%)	41 (93.2%)
Perirectal	0	1 (4.8%)	0	1 (3.6%)	0	1 (2.3%)
Other	1 (14.3%)	0	1 (14.3%)	1 (3.6%)	2 (22.2%)	4 (9.1%)

Table 26: CD related baseline disease characteristics – GALAXI 3 study

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	143	150	293	148	513
Crohn's disease duration (years)						
N	72	143	150	293	148	513
Mean (SD)	7.97 (7.545)	6.33 (6.083)	6.84 (7.748)	6.59 (6.978)	8.02 (8.270)	7.20 (7.469)
Median	5.65	4.50	3.61	3.93	5.58	4.74
Range	(0.3; 44.2)	(0.2; 30.6)	(0.3; 39.9)	(0.2; 39.9)	(0.3; 38.3)	(0.2; 44.2)
IQ range	(2.95; 11.25)	(1.61; 9.78)	(1.56; 8.63)	(1.59; 8.85)	(2.00; 10.68)	(1.77; 10.31)
≤ 5 years	31 (43.1%)	77 (53.8%)	91 (60.7%)	168 (57.3%)	68 (45.9%)	267 (52.0%)
>5 and ≤ 15 years	30 (41.7%)	52 (36.4%)	37 (24.7%)	89 (30.4%)	58 (39.2%)	177 (34.5%)
>15 years	11 (15.3%)	14 (9.8%)	22 (14.7%)	36 (12.3%)	22 (14.9%)	69 (13.5%)
CDAI Score						
N	72	143	150	293	148	513
Mean (SD)	294.9 (54.09)	295.3 (56.09)	297.6 (53.85)	296.4 (54.87)	291.0 (51.73)	294.7 (53.83)
Median	279.0	287.0	288.0	288.0	287.0	286.0
Range	(223; 442)	(220; 442)	(221; 440)	(220; 442)	(204; 439)	(204; 442)
IQ range	(250.0; 337.0)	(249.0; 332.0)	(257.0; 336.0)	(252.0; 335.0)	(246.0; 327.5)	(250.0; 332.0)
Stool frequency count > 3	55 (76.4%)	105 (73.4%)	120 (80.0%)	225 (76.8%)	115 (77.7%)	395 (77.0%)
Abdominal pain score > 1	67 (93.1%)	136 (95.1%)	145 (96.7%)	281 (95.9%)	141 (95.3%)	489 (95.3%)
Stool frequency count > 3 and Abdominal pain score > 1	50 (69.4%)	98 (68.5%)	115 (76.7%)	213 (72.7%)	108 (73.0%)	371 (72.3%)
SES-CD						
N	72	143	150	293	148	513
Mean (SD)	12.7 (7.27)	13.4 (7.83)	12.6 (7.37)	13.0 (7.59)	12.4 (6.55)	12.8 (7.25)
Median	11.0	11.0	11.0	11.0	11.0	11.0
Range	(4; 37)	(4; 42)	(4; 37)	(4; 42)	(4; 37)	(4; 42)
IQ range	(7.0; 17.0)	(7.0; 18.0)	(6.0; 17.0)	(7.0; 17.0)	(7.0; 16.0)	(7.0; 17.0)
Endoscopic disease severity per SES-CD score						
N	72	143	150	293	148	513
< 7	14 (19.4%)	20 (14.0%)	41 (27.3%)	61 (20.8%)	31 (20.9%)	106 (20.7%)
7-16	39 (54.2%)	81 (56.6%)	68 (45.3%)	149 (50.9%)	84 (56.8%)	272 (53.0%)
> 16	19 (26.4%)	42 (29.4%)	41 (27.3%)	83 (28.3%)	33 (22.3%)	135 (26.3%)

CRP concentration (mg/L)						
N	72	143	150	293	148	513
Mean (SD)	14.5 (22.40)	18.5 (22.71)	16.4 (22.96)	17.4 (22.82)	15.9 (23.97)	16.6 (23.08)
Median	5.5	7.8	6.4	7.3	6.6	6.7
Range	(0; 111)	(0; 128)	(0; 133)	(0; 133)	(0; 157)	(0; 157)
IQ range	(1.4; 16.1)	(3.0; 27.6)	(3.0; 22.6)	(3.0; 24.3)	(2.0; 21.5)	(2.4; 22.6)
≤ 3	25 (34.7%)	35 (24.5%)	39 (26.0%)	74 (25.3%)	51 (34.5%)	150 (29.2%)
> 3	47 (65.3%)	108 (75.5%)	111 (74.0%)	219 (74.7%)	97 (65.5%)	363 (70.8%)
Fecal calprotectin (µg/g)						
N	71	141	149	290	146	507
Mean (SD)	1965.5 (3168.06)	1687.3 (1783.88)	2021.6 (3735.02)	1859.1 (2951.90)	1554.2 (2083.59)	1786.2 (2762.68)
Median	962.0	994.0	1242.0	1107.0	773.0	983.0
Range	(15; 17983)	(15; 10630)	(15; 36000)	(15; 36000)	(15; 13689)	(15; 36000)
IQ range	(255.0; 2481.0)	(499.0; 2394.0)	(361.0; 2167.0)	(410.0; 2311.0)	(323.0; 1855.0)	(357.0; 2169.0)
≤ 250	17 (23.9%)	25 (17.7%)	26 (17.4%)	51 (17.6%)	31 (21.2%)	99 (19.5%)
> 250	54 (76.1%)	116 (82.3%)	123 (82.6%)	239 (82.4%)	115 (78.8%)	408 (80.5%)
Fecal calprotectin >250 µg/g and CRP >3 mg/L						
N	71	141	149	290	146	507
Yes	39 (54.9%)	94 (66.7%)	101 (67.8%)	195 (67.2%)	84 (57.5%)	318 (62.7%)
No	32 (45.1%)	47 (33.3%)	48 (32.2%)	95 (32.8%)	62 (42.5%)	189 (37.3%)
IBDQ						
N	71	140	147	287	143	501
Mean (SD)	129.4 (37.76)	126.4 (31.72)	126.0 (28.21)	126.2 (29.92)	129.2 (31.43)	127.5 (31.54)
Median	130.0	127.5	125.0	127.0	129.0	127.0
Range	(55; 213)	(49; 201)	(60; 188)	(49; 201)	(52; 201)	(49; 213)
IQ range	(103.0; 152.0)	(104.5; 148.5)	(109.0; 143.0)	(107.0; 146.0)	(107.0; 146.0)	(106.0; 147.0)
Involved GI areas (assessed by central reader)						
N	72	143	150	293	148	513
Ileum only	14 (19.4%)	30 (21.0%)	41 (27.3%)	71 (24.2%)	30 (20.3%)	115 (22.4%)
Colon only	33 (45.8%)	51 (35.7%)	56 (37.3%)	107 (36.5%)	58 (39.2%)	198 (38.6%)
Ileum and Colon	25 (34.7%)	62 (43.4%)	53 (35.3%)	115 (39.2%)	60 (40.5%)	200 (39.0%)
Number of subjects with at least 1 open or draining fistula	12 (16.7%)	23 (16.1%)	17 (11.3%)	40 (13.7%)	16 (10.8%)	68 (13.3%)
1 fistula	10 (13.9%)	17 (11.9%)	15 (10.0%)	32 (10.9%)	12 (8.1%)	54 (10.5%)
>1 fistulas	2 (2.8%)	6 (4.2%)	2 (1.3%)	8 (2.7%)	4 (2.7%)	14 (2.7%)
Number of subjects with at least 1 open or draining fistula	12	23	17	40	16	68
Median	1.0	1.0	1.0	1.0	1.0	1.0
Range	(1; 4)	(1; 3)	(1; 3)	(1; 3)	(1; 4)	(1; 4)
Perianal	11 (91.7%)	19 (82.6%)	14 (82.4%)	33 (82.5%)	13 (81.3%)	57 (83.8%)
Perirectal	0	1 (4.3%)	0	1 (2.5%)	1 (6.3%)	2 (2.9%)
Other	1 (8.3%)	3 (13.0%)	3 (17.6%)	6 (15.0%)	4 (25.0%)	11 (16.2%)

Concomitant medication (CD-related)

Table 27: Summary of Concomitant Medications for CD at Baseline; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	76	143	146	289	143	508
Subjects with 1 or more concomitant medications for Crohn's disease	47 (61.8%)	106 (74.1%)	108 (74.0%)	214 (74.0%)	109 (76.2%)	370 (72.8%)
Immunomodulatory drugs	21 (27.6%)	43 (30.1%)	46 (31.5%)	89 (30.8%)	42 (29.4%)	152 (29.9%)
6-mercaptopurine/azathioprine	18 (23.7%)	43 (30.1%)	45 (30.8%)	88 (30.4%)	39 (27.3%)	145 (28.5%)
Methotrexate	3 (3.9%)	0	1 (0.7%)	1 (0.3%)	3 (2.1%)	7 (1.4%)
Oral aminosalicylates	23 (30.3%)	62 (43.4%)	61 (41.8%)	123 (42.6%)	64 (44.8%)	210 (41.3%)
Antibiotics	4 (5.3%)	6 (4.2%)	12 (8.2%)	18 (6.2%)	6 (4.2%)	28 (5.5%)
Oral corticosteroid use	25 (32.9%)	54 (37.8%)	55 (37.7%)	109 (37.7%)	56 (39.2%)	190 (37.4%)
Corticosteroid use (excl. budesonide and beclomethasone dipropionate)	17 (22.4%)	39 (27.3%)	33 (22.6%)	72 (24.9%)	38 (26.6%)	127 (25.0%)
Budesonide	8 (10.5%)	17 (11.9%)	22 (15.1%)	39 (13.5%)	18 (12.6%)	65 (12.8%)
Beclomethasone dipropionate	0	0	0	0	0	0
Corticosteroid dose, mg (excluding budesonide and beclomethasone diproprionate)						
N	17	39	33	72	38	127
Mean (SD)	18.2 (8.65)	17.5 (9.64)	18.7 (9.47)	18.1 (9.51)	17.1 (8.27)	17.8 (8.99)
Median	15.0	20.0	20.0	20.0	20.0	20.0
Range	(10; 40)	(3; 40)	(5; 40)	(3; 40)	(5; 40)	(3; 40)
IQ range	(10.0; 20.0)	(10.0; 20.0)	(12.5; 20.0)	(10.0; 20.0)	(10.0; 20.0)	(10.0; 20.0)
Budesonide dose, mg						
N	8	17	22	39	18	65
Mean (SD)	7.5 (2.27)	8.5 (1.59)	7.6 (2.29)	8.0 (2.04)	8.3 (1.28)	8.0 (1.88)
Median	9.0	9.0	9.0	9.0	9.0	9.0
Range	(3; 9)	(3; 9)	(3; 9)	(3; 9)	(6; 9)	(3; 9)
IQ range	(6.0; 9.0)	(9.0; 9.0)	(6.0; 9.0)	(9.0; 9.0)	(9.0; 9.0)	(9.0; 9.0)

Table 28: Summary of Concomitant Medications for CD at Baseline; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	143	150	293	148	513
Subjects with 1 or more concomitant medications for Crohn's disease	49 (68.1%)	101 (70.6%)	109 (72.7%)	210 (71.7%)	101 (68.2%)	360 (70.2%)
Immunomodulatory drugs	19 (26.4%)	44 (30.8%)	51 (34.0%)	95 (32.4%)	41 (27.7%)	155 (30.2%)
6-mercaptopurine/azathioprine	18 (25.0%)	42 (29.4%)	44 (29.3%)	86 (29.4%)	40 (27.0%)	144 (28.1%)
Methotrexate	1 (1.4%)	2 (1.4%)	6 (4.0%)	8 (2.7%)	1 (0.7%)	10 (1.9%)
Oral aminosalicylates	21 (29.2%)	59 (41.3%)	55 (36.7%)	114 (38.9%)	55 (37.2%)	190 (37.0%)
Antibiotics	3 (4.2%)	6 (4.2%)	6 (4.0%)	12 (4.1%)	8 (5.4%)	23 (4.5%)
Oral corticosteroid use	26 (36.1%)	55 (38.5%)	51 (34.0%)	106 (36.2%)	53 (35.8%)	185 (36.1%)
Corticosteroid use (excl. budesonide and beclomethasone dipropionate)	16 (22.2%)	36 (25.2%)	35 (23.3%)	71 (24.2%)	35 (23.6%)	122 (23.8%)
Budesonide	10 (13.9%)	19 (13.3%)	16 (10.7%)	35 (11.9%)	18 (12.2%)	63 (12.3%)
Beclomethasone dipropionate	0	0	0	0	0	0
Corticosteroid dose, mg (excluding budesonide and beclomethasone diproprionate)						
N	16	36	35	71	35	122
Mean (SD)	22.3 (10.47)	19.6 (9.96)	21.0 (10.56)	20.3 (10.21)	18.1 (9.30)	19.9 (10.00)
Median	20.0	20.0	20.0	20.0	20.0	20.0
Range	(5; 40)	(5; 40)	(5; 40)	(5; 40)	(3; 40)	(3; 40)
IQ range	(17.5; 27.5)	(10.0; 20.0)	(15.0; 20.0)	(15.0; 20.0)	(10.0; 20.0)	(10.0; 20.0)
Budesonide dose, mg						
N	10	19	16	35	18	63
Mean (SD)	8.4 (1.26)	7.9 (2.28)	7.6 (2.29)	7.8 (2.26)	7.5 (2.36)	7.8 (2.15)
Median	9.0	9.0	9.0	9.0	9.0	9.0
Range	(6; 9)	(3; 9)	(3; 9)	(3; 9)	(3; 9)	(3; 9)
IQ range	(9.0; 9.0)	(9.0; 9.0)	(6.0; 9.0)	(6.0; 9.0)	(6.0; 9.0)	(6.0; 9.0)

Prior medication – CD related

GALAXI 2

- 52.8% of participants had a history of inadequate response or intolerance to previous biologic medication treatment (BIO-Failure group). Proportions were similar across treatment groups (ranging from 50.0% to 55.2%).

- 47.2% of participants had a history of inadequate response to conventional therapy but not biologic therapy (CON-Failure subpopulation). Proportions were similar across treatment groups (ranging from 44.8% to 50.0%).
- 41.9% of participants were naïve to biologic therapy (BIO-Naive subpopulation). Proportions were similar across treatment groups (ranging from 40.6% to 44.7%). The BIO-Naive subpopulation is a subset of the CON-Failure subpopulation.
- 0.8% of participants had previously used ustekinumab (1 participant each in the placebo treatment group and ustekinumab treatment group, and 2 participants in the guselkumab 200 mg SC q4w treatment group).

Table 29: CD related Biologic medication history – GALAXI 2

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	76	143	146	289	143	508
Subjects without a history of biologic failure	37 (48.7%)	66 (46.2%)	73 (50.0%)	139 (48.1%)	64 (44.8%)	240 (47.2%)
Biologic-naive	34 (44.7%)	58 (40.6%)	63 (43.2%)	121 (41.9%)	58 (40.6%)	213 (41.9%)
Biologic-experienced, but not documented failure	3 (3.9%)	8 (5.6%)	10 (6.8%)	18 (6.2%)	6 (4.2%)	27 (5.3%)
Subjects with a history of biologic failure	39 (51.3%)	77 (53.8%)	73 (50.0%)	150 (51.9%)	79 (55.2%)	268 (52.8%)
Primary nonresponse, secondary nonresponse, or intolerance to						
At least one anti-TNF	39 (51.3%)	74 (51.7%)	71 (48.6%)	145 (50.2%)	73 (51.0%)	257 (50.6%)
Two or more anti-TNFs	10 (13.2%)	16 (11.2%)	15 (10.3%)	31 (10.7%)	25 (17.5%)	66 (13.0%)
Anti-TNF only	35 (46.1%)	64 (44.8%)	65 (44.5%)	129 (44.6%)	66 (46.2%)	230 (45.3%)
Vedolizumab	4 (5.3%)	13 (9.1%)	8 (5.5%)	21 (7.3%)	13 (9.1%)	38 (7.5%)
Vedolizumab only	0	3 (2.1%)	2 (1.4%)	5 (1.7%)	6 (4.2%)	11 (2.2%)
Vedolizumab and at least one anti-TNF	4 (5.3%)	10 (7.0%)	6 (4.1%)	16 (5.5%)	7 (4.9%)	27 (5.3%)

GALAXI 3

- 51.9% of participants had a history of inadequate response or intolerance to previous biologic medication treatment (BIO-Failure subpopulation).
- 48.1% of participants had a history of inadequate response to conventional therapy but not biologic therapy (CON-Failure subpopulation). Proportions were similar across treatment groups (ranging from 45.8% to 50.7%).
- 41.5% of participants were naïve to biological therapy (BIO-Naïve subpopulation). Proportions were similar across treatment groups (ranging from 37.5% to 43.3%). The BIO-Naïve subpopulation is a subset of the CON-Failure subpopulation.
- 1.8% of participants had previously used ustekinumab but did not experience failure or intolerance (3 participants in the guselkumab 200 mg SC q4w treatment group, 1 participant each in the placebo treatment group and guselkumab 100 mg SC q8w treatment group, and 4 participants in the ustekinumab treatment group).

Table 30: CD related Biologic medication history – GALAXI 3

		Guselkumab				
	Placebo[a]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w	Total
Analysis set: Primary	72	143	150	293	148	513
Subjects without a history of biologic failure	33 (45.8%)	67 (46.9%)	76 (50.7%)	143 (48.8%)	71 (48.0%)	247 (48.1%)
Biologic-naive	27 (37.5%)	58 (40.6%)	65 (43.3%)	123 (42.0%)	63 (42.6%)	213 (41.5%)
Biologic-experienced, but not documented failure	6 (8.3%)	9 (6.3%)	11 (7.3%)	20 (6.8%)	8 (5.4%)	34 (6.6%)
Subjects with a history of biologic failure	39 (54.2%)	76 (53.1%)	74 (49.3%)	150 (51.2%)	77 (52.0%)	266 (51.9%)
Primary nonresponse, secondary nonresponse, or intolerance to						
At least one anti-TNF	37 (51.4%)	75 (52.4%)	72 (48.0%)	147 (50.2%)	74 (50.0%)	258 (50.3%)
Two or more anti-TNFs	13 (18.1%)	15 (10.5%)	16 (10.7%)	31 (10.6%)	21 (14.2%)	65 (12.7%)
Anti-TNF only	30 (41.7%)	64 (44.8%)	64 (42.7%)	128 (43.7%)	59 (39.9%)	217 (42.3%)
Vedolizumab	9 (12.5%)	12 (8.4%)	10 (6.7%)	22 (7.5%)	18 (12.2%)	49 (9.6%)
Vedolizumab only	2 (2.8%)	1 (0.7%)	2 (1.3%)	3 (1.0%)	3 (2.0%)	8 (1.6%)
Vedolizumab and at least one anti-TNF	7 (9.7%)	11 (7.7%)	8 (5.3%)	19 (6.5%)	15 (10.1%)	41 (8.0%)

Numbers analysed

In Study GALAXI 2, 524 participants were randomized, and 523 participants were treated. Of the treated patients, 148, 149, 150 and 77 participants were randomized to the guselkumab 200 mg SC Q4W, guselkumab 100 mg SC Q8W, ustekinumab and placebo treatment groups, respectively.

In Study GALAXI 3, 525 participants were randomized and treated. Of them, 151, 148, 150 and 76 participants were randomized to the guselkumab 200 mg SC Q4W, guselkumab 100 mg SC Q8W, ustekinumab placebo treatment groups, respectively.

Outcomes and estimation

2.4.2.1.1. Results for study GALAXI 2

Co-Primary Endpoints – Clinical Remission at Week 12 and Endoscopic Response Week 12

Table 31: Summary of the Region-specific Co-Primary Endpoints; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	76	289
Clinical remission at Week 12	22.4%	47.1%*
Endoscopic response at Week 12	10.5%	37.7%*

* significant p-values (relative to placebo) based on the testing procedure

The proportions of participants with ICEs prior to Week 12 were 3.1% in the combined guselkumab 200 mg IV treatment group and 9.2% in the placebo treatment group. The number (proportions) of participants with missing data, after accounting for ICE strategies, was 0 (0%) for the clinical remission at Week 12 co-primary endpoint, and 7 (1.9%) for the endoscopic response at Week 12 co-primary endpoint.

Major Secondary Endpoints

Short-term Week 12 Comparisons

Table 32: Summary of the Region-specific Major Secondary Endpoints With Short-term Placebo-based Comparisons (Set 1); Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	76	289
PRO-2 remission at Week 12	21.1%	42.9%*
Fatigue response at Week 12	28.9%	45.3%*
Endoscopic remission (Region-Specific) at Week 12	1.3%	14.9%†

* significant p-values (relative to placebo) based on the testing procedure; † nominal p<0.05

A subgroup analysis was also performed among those participants who had a baseline mean daily SF score of at least 4 or AP score of at least 2. The proportions of participants in PRO-2 remission at Week 12 in the combined guselkumab 200 mg IV treatment group (40.5%) and the placebo treatment group (20.0%) were similar to the main analysis above (42.9% and 21.1%, respectively).

Long-term Week 48 Comparisons vs Placebo

Table 33: Summary of the Major Secondary Endpoints With Long-term Placebo-based Comparisons (Set 2); Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

		Guselkumab	
	Placebo	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w
Analysis set: Primary	76	143	146
Corticosteroid-free clinical remission at Week 48	11.8%	45.5%*	51.4%*
Endoscopic response at Week 48	6.6%	38.5%*	38.4%*

* significant p-values (relative to placebo) based on the testing procedure

Efficacy Results (Guselkumab vs Ustekinumab)

Table 34: Summary of the Major Secondary Endpoints With Long-term Ustekinumab-based Comparisons (Set 3); Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

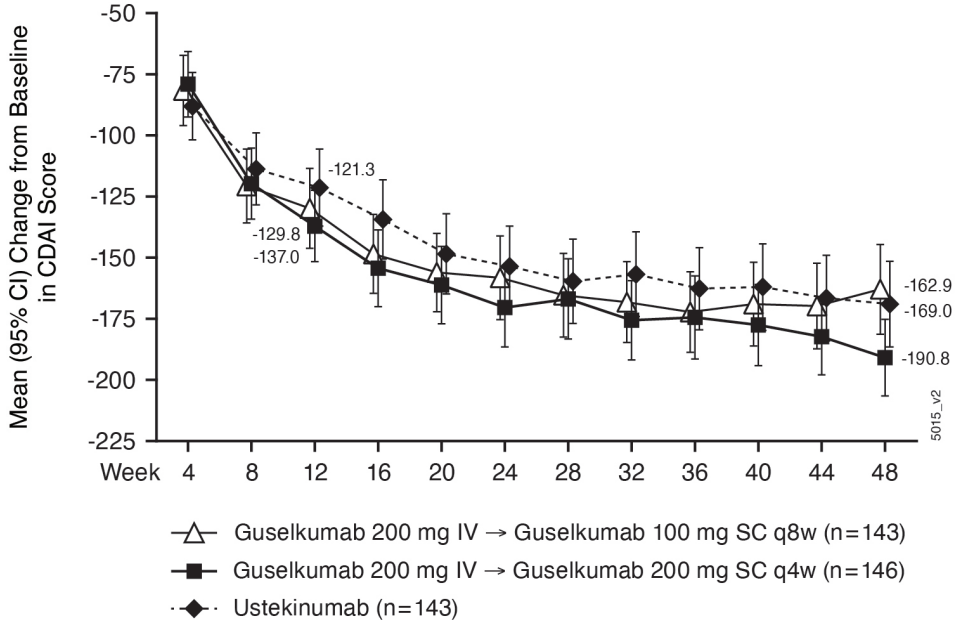
	Guselkumab		
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Primary	143	146	143
Clinical remission at Week 48 and endoscopic response at Week 48	42.0%	49.3%	39.2%
Endoscopic remission (Region-Specific) at Week 48	26.6%	24.0%	20.3%
Clinical remission at Week 48	64.3%	74.7%	65.0%
Endoscopic response at Week 48	49.0%	56.2%†	42.0%
PRO-2 remission at Week 48	60.1%	69.2%	59.4%
Corticosteroid-free clinical remission at Week 48	62.9%	71.2%	60.8%
Durable clinical remission at Week 48	46.2%	52.1%	44.8%

† nominal p<0.05

A subgroup analysis was also performed among those participants who had a baseline mean daily SF score of at least 4 or AP score of at least 2. The proportion of participants in PRO-2 remission at Week 48 for the guselkumab 200 mg SC q4w treatment group (59.2%), the guselkumab 100 mg SC q8w treatment group (65.6%), and the ustekinumab treatment group (60.6%) was similar to the main analysis above (60.1%, 69.2%, and 59.4%, respectively).

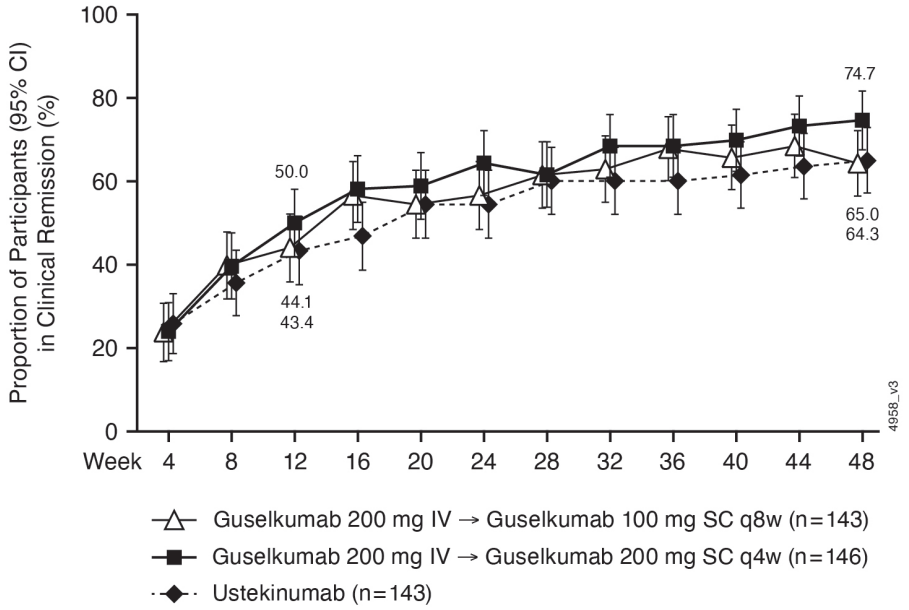
Other Efficacy Analyses

Figure 25: Line Plot of Mean (95% CI) for Change from Baseline in CDAI by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



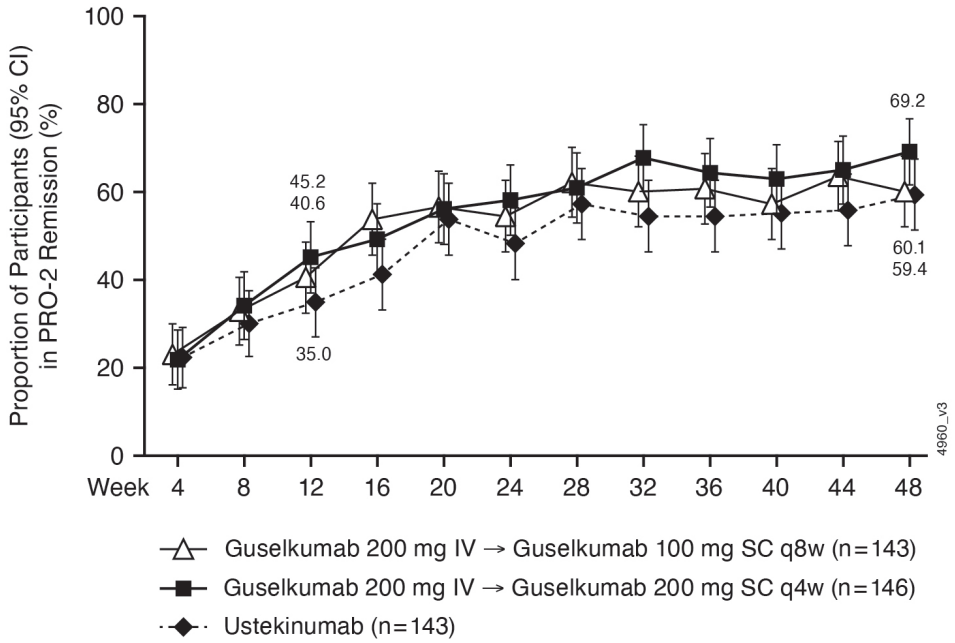
Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 26: Line Plot of Proportion of Subjects in Clinical Remission by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 27: Line Plot of Proportion of Participants in PRO-2 Remission by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



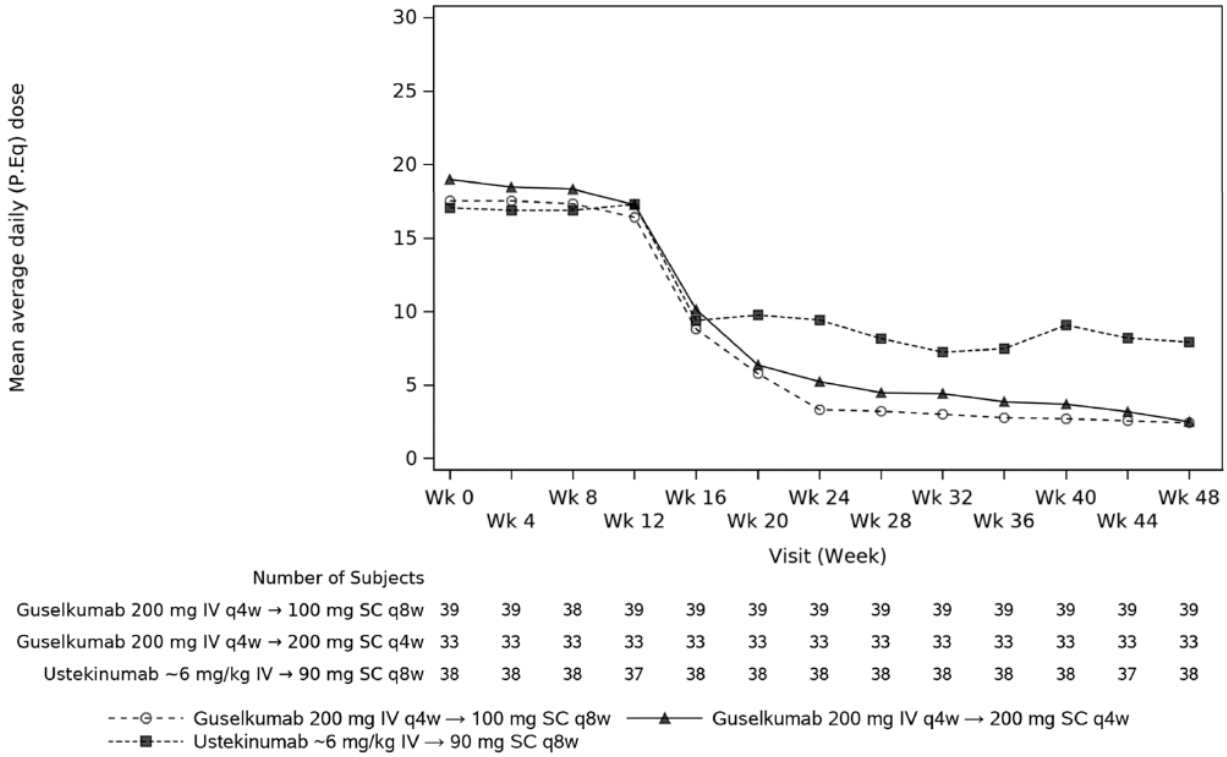
Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Corticosteroid-Related Endpoints

Over a third of the population was receiving corticosteroids at baseline. Among participants receiving corticosteroids at baseline, the proportions of participants who were able to eliminate corticosteroids at Week 48 were 83.6% in the guselkumab 200 mg SC q4w treatment group, 72.2% in the guselkumab 100 mg SC q8w treatment group, and 62.5% in the ustekinumab treatment group.

Additionally, among participants receiving corticosteroids at baseline, 67.3% of participants in the guselkumab 200 mg SC q4w treatment group, 55.6% of participants in the guselkumab 100 mg SC q8w treatment group, and 57.1% of participants in the ustekinumab treatment group achieved corticosteroid-free clinical remission at Week 48.

Figure 28: Line Plot of Average Daily Prednisone-equivalent Dose (Excluding Budesonide and Beclomethasone Dipropionate) by Visit Through Week 48 Among Those Receiving Oral Corticosteroids other Than Budesonide or Beclomethasone Dipropionate at Baseline; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



Inflammatory Biomarker Endpoints

Greater changes from baseline in inflammatory biomarkers (CRP and fecal calprotectin) were observed in the combined guselkumab 200 mg IV treatment group as early as Week 4 and continued to decrease through Week 12 as compared with the placebo treatment group. The change from baseline in the guselkumab treatment groups was generally maintained through Week 48.

Patient-reported Outcomes

Abdominal Pain

Proportions of participants with baseline average daily abdominal pain scores >1 (based on CDAI) achieving an average daily abdominal pain score ≤1 were as follows:

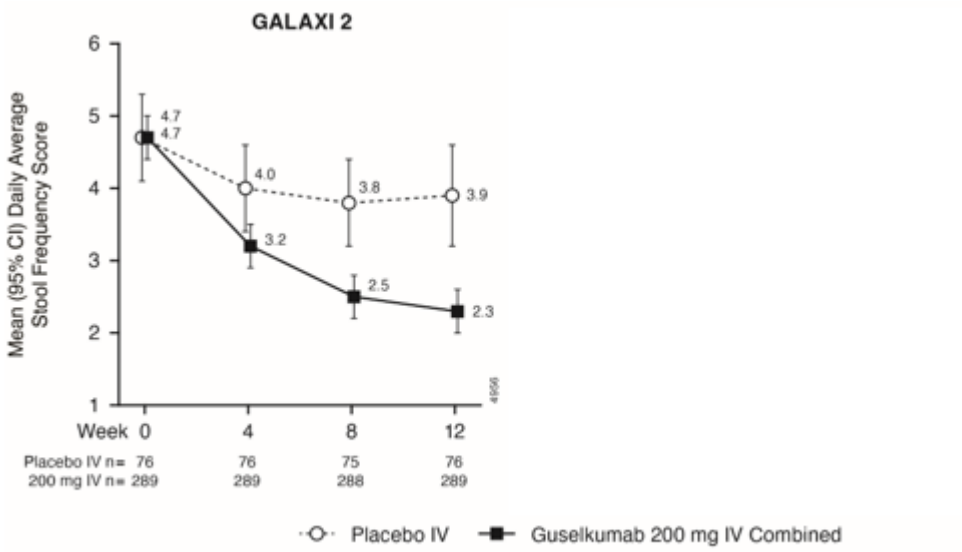
- Week 12
    - combined guselkumab 200 mg IV treatment group: 50.4%
    - placebo treatment group: 29.6%
    - ustekinumab i.v. treatment group: 43.6%.
- Week 48
    - guselkumab 200 mg SC q4w treatment group: 79.3%
    - guselkumab 100 mg SC q8w treatment group: 64.0%
    - ustekinumab treatment group: 70.7%

Stool Frequency

Proportions of participants with an average daily number of liquid or very soft stools >3 at baseline (based on CDAI) who had an average daily number of liquid or very soft stools ≤3 were as follows:

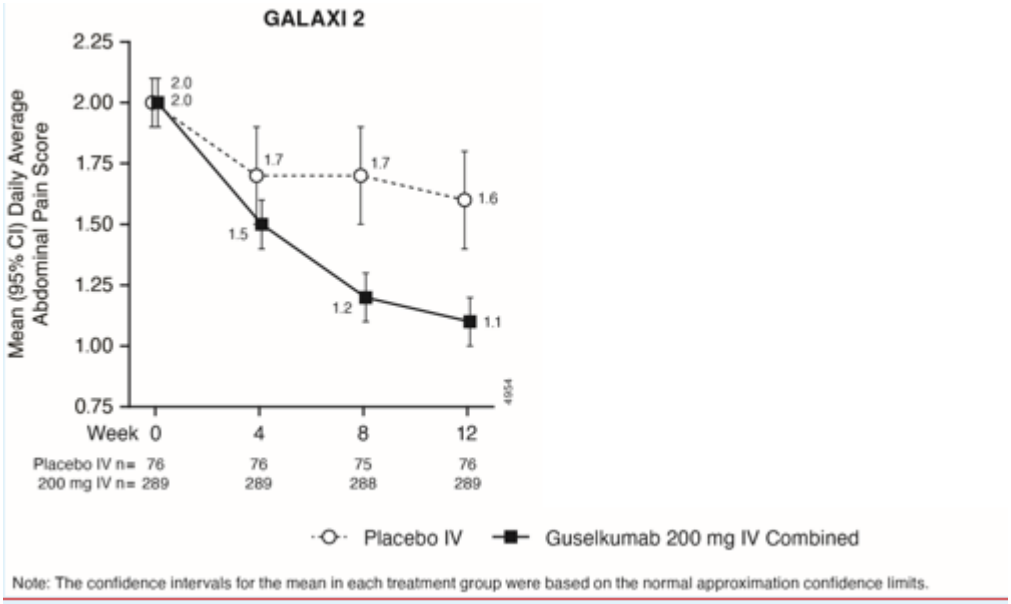
- Week 12
    - combined guselkumab 200 mg IV treatment group: 61.5%
    - placebo treatment group: 33.9%.
    - ustekinumab i.v. treatment group: 52.8%.
- Week 48
    - guselkumab 200 mg SC q4w treatment group: 75.0%
    - guselkumab 100 mg SC q8w treatment group: 70.4%
    - ustekinumab treatment group: 65.7%

Figure 29: Mean (95% CI) Daily Average Stool Frequency Through Week 12; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



Note: The confidence intervals for the mean in each treatment group were based on the normal approximation confidence limits.

Figure 30: Mean (95% CI) Daily Average Abdominal Pain Score Through Week 12; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)



Note: The confidence intervals for the mean in each treatment group were based on the normal approximation confidence limits.

Fatigue

Table 35: PROMIS-Fatigue SF 7a T-scores at Week 12 and Week 48 (Study GALAXI 2)

	Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Week 12[a,b]				
N	141	142	283	139
Mean (SD)	-7.02 (7.619)	-6.67 (9.014)	-6.85 (8.335)	-5.90 (8.129)
Median	-5.60	-5.60	-5.60	-5.50
Range	(-29.0; 8.3)	(-38.4; 15.1)	(-38.4; 15.1)	(-29.4; 17.8)
IQ range	(-11.80; -1.40)	(-12.00; -1.40)	(-11.90; -1.40)	(-10.60; 0.00)
N[c]	142	143	285	140
LS Means (SE)[d]	-6.79 (0.633)	-7.16 (0.634)	-6.97 (0.453)	-5.82 (0.637)
LS Mean Difference (95% CI) from Ustekinumab[d]	0.97 (-0.77, 2.71)	1.34 (-0.41, 3.08)	1.15 (-0.36, 2.66)	
p-value[d]	0.275	0.133	0.134	
Week 48[a,b]				
N	142	138	280	139
Mean (SD)	-7.77 (9.633)	-8.41 (8.788)	-8.08 (9.215)	-7.82 (8.113)
Median	-6.30	-7.50	-7.20	-6.90
Range	(-49.8; 11.1)	(-34.4; 15.5)	(-49.8; 15.5)	(-25.5; 8.9)
IQ range	(-13.90; 0.00)	(-13.90; -1.30)	(-13.90; 0.00)	(-14.10; 0.00)
N[c]	142	143	285	140
LS Means (SE)[d]	-7.56 (0.684)	-8.87 (0.692)	-8.20 (0.492)	-7.79 (0.690)
LS Mean Difference (95% CI) from Ustekinumab[d]	-0.24 (-2.13, 1.65)	1.08 (-0.82, 2.98)	0.41 (-1.24, 2.05)	
p-value[d]	0.805	0.266	0.626	

Key: ICE=intercurrent event

a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional

crisis [ICE5] prior to the analysis timepoint had their baseline value carried forward. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available.

b Missing data imputation: After accounting for ICE strategies, subjects who were missing PROMIS-29 score at the designated analysis timepoint did not have their missing data imputed.

c Number of subjects with baseline value and at least one post-baseline visit value.

d The LS Mean and SE for each treatment group, LS Mean difference between the treatment groups and p-values for the comparisons of each guselkumab treatment group with the ustekinumab group were based on MMRM analysis including change from baseline in PROMIS-29 score as the response; treatment group, visit, baseline PROMIS-29 score, BIO-Failure status (Yes, No), baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), baseline corticosteroid use (Yes or No), an interaction term of visit with treatment group and an interaction term of visit with baseline PROMIS-29 score as explanatory variables.

Improvement in Health-related Quality of Life

PROMIS-29

At Week 12, the combined guselkumab 200 mg IV treatment group had greater improvements from baseline in the mean scores for pain intensity NRS, physical and mental health summary (PCS and MCS), and 6 of the 7 PROMIS-29 domains (depression, anxiety, fatigue, pain interference, physical function, ability to participate in social roles and activities) compared with the placebo treatment group.

At Week 48, the MAH considered that the proportions of participants who achieved improved PROMIS-29 scores were similar between the guselkumab treatment groups and the ustekinumab treatment group.

IBDQ

IBDQ remission:

- Week 12
    - combined guselkumab 200 mg IV treatment group: 44.6%
    - placebo treatment group: 30.3%.
    - ustekinumab i.v. treatment group: 39.9%.
- Week 48
    - guselkumab 200 mg SC q4w treatment group: 57.5%
    - guselkumab 100 mg SC q8w treatment group: 53.8%
    - ustekinumab treatment group: 52.4%

Table 36: Summary of Change From Baseline in IBDQ Total Score and Dimensions by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2)

	Guselkumab			Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	
Analysis set: Primary	143	146	289	143
IBDQ Total Score				
Baseline				
N	142	143	285	140
Mean (SD)	123.8 (33.17)	128.0 (30.07)	125.9 (31.67)	127.5 (30.54)
Median	124.0	125.0	124.0	126.0
Range	(46; 205)	(56; 202)	(46; 205)	(49; 213)
IQ range	(103.0; 145.0)	(106.0; 146.0)	(105.0; 145.0)	(107.5; 147.0)
Week 8[a,b]				
N	137	138	275	134
Mean (SD)	157.2 (33.67)	159.7 (32.53)	158.4 (33.07)	156.4 (32.54)
Median	163.0	162.5	163.0	159.5
Range	(43; 221)	(78; 223)	(43; 223)	(72; 222)
IQ range	(137.0; 184.0)	(134.0; 185.0)	(135.0; 185.0)	(134.0; 182.0)
Week 12[a,b]				
N	142	143	285	140
Mean (SD)	162.9 (32.19)	161.3 (32.44)	162.1 (32.27)	158.4 (33.72)
Median	165.0	160.0	163.0	159.5
Range	(69; 220)	(73; 223)	(69; 223)	(60; 222)
IQ range	(143.0; 189.0)	(140.0; 188.0)	(141.0; 188.0)	(137.5; 185.0)
Week 24[a,b]				
N	138	137	275	139
Mean (SD)	167.9 (35.46)	171.3 (29.23)	169.6 (32.50)	167.9 (33.85)
Median	174.0	173.0	174.0	173.0
Range	(46; 224)	(89; 224)	(46; 224)	(73; 224)
IQ range	(150.0; 197.0)	(149.0; 192.0)	(149.0; 194.0)	(142.0; 195.0)
Week 48[a,b]				
N	143	139	282	143
Mean (SD)	167.4 (37.14)	175.6 (31.55)	171.5 (34.68)	169.2 (35.54)
Median	174.0	179.0	176.0	176.0
Range	(46; 224)	(89; 224)	(46; 224)	(59; 224)

EQ-5D/EQ-VAS

Improvements observed in EQ-5D (mobility, pain/discomfort, usual activities and anxiety/depression) and EQ-VAS were greater in the combined guselkumab 200 mg IV treatment group at Week 12 compared with the placebo treatment group. At Week 48, similar proportions of participants in the guselkumab and ustekinumab treatment groups achieved improved status in the EQ-5D dimensions.

2.4.2.1.2. Results for study GALAXI 3

Co-Primary Endpoints – Clinical Remission at Week 12 and Endoscopic Response Week 12

Table 37: Summary of the Region-specific Co-Primary Endpoints; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	72	293
Clinical remission at Week 12	15.3%	47.1%*
Endoscopic response at Week 12	13.9%	36.2%*

* significant p-values (relative to placebo) based on the testing procedure

The proportions of participants with ICEs prior to Week 12 were 7.5% in the combined guselkumab 200 mg IV treatment group and 13.9% in the placebo treatment group. The number (proportions) of participants with missing data, after accounting for ICE strategies, was 1 (0.3%) for the clinical remission at Week 12 co-primary endpoint, and 2 (0.5%) for the endoscopic response at Week 12 co-primary endpoint.

Three prespecified sensitivity analyses (with different approaches for handling missing data) were performed. The results of these analyses confirmed the robustness of the co-primary endpoints.

Supplementary estimand analyses were also performed and the results were the same as the primary estimands.

Major Secondary Endpoints

Short-term Week 12 Comparisons

Table 38: Summary of the Region-specific Major Secondary Endpoints With Short-term Placebo-based Comparisons (Set 1); Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	72	293
PRO-2 remission at Week 12	13.9%	41.6%*
Fatigue response at Week 12	18.1%	43.3%*
Endoscopic remission (Region-Specific) at Week 12	8.3%	16.0%

* significant p-values (relative to placebo) based on the testing procedure

A subgroup analysis was also performed among those participants who had a baseline mean daily SF score of at least 4 or AP score of at least 2. The proportions of participants in PRO-2 remission at Week 12 in the combined guselkumab 200 mg IV treatment group (38.3%) and the placebo treatment group (8.1%) were similar to the main analysis above (41.6% and 13.9%, respectively).

Long-term Week 48 Comparisons vs Placebo

Table 39: Summary of the Region-specific Major Secondary Endpoints With Long-term Placebo-based Comparisons (Set 2); Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

	Placebo	Guselkumab 200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w
Analysis set: Primary	72	143	150
Corticosteroid-free clinical remission at Week 48	13.9%	44.1%*	48.0%*
Endoscopic response at Week 48	5.6%	32.9%*	36.0%*

* significant p-values (relative to placebo) based on the testing procedure

Efficacy Results (Guselkumab vs Ustekinumab)

Table 40: Summary of the Region-specific Major Secondary Endpoints With Long-term Ustekinumab-based Comparisons (Set 3); Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Clinical remission at Week 48 and endoscopic response at Week 48	41.3%*	45.3%*	28.4%
Endoscopic remission (Region-Specific) at Week 48	23.8%*	18.7%	12.8%
Clinical remission at Week 48	66.4%	66.0%	60.8%
Endoscopic response at Week 48	46.9%†	49.3%†	32.4%
PRO-2 remission at Week 48	58.0%	56.0%	52.7%
Corticosteroid-free clinical remission at Week 48	64.3%	64.0%	58.8%
Durable clinical remission at Week 48	50.3%	48.7%	39.2%

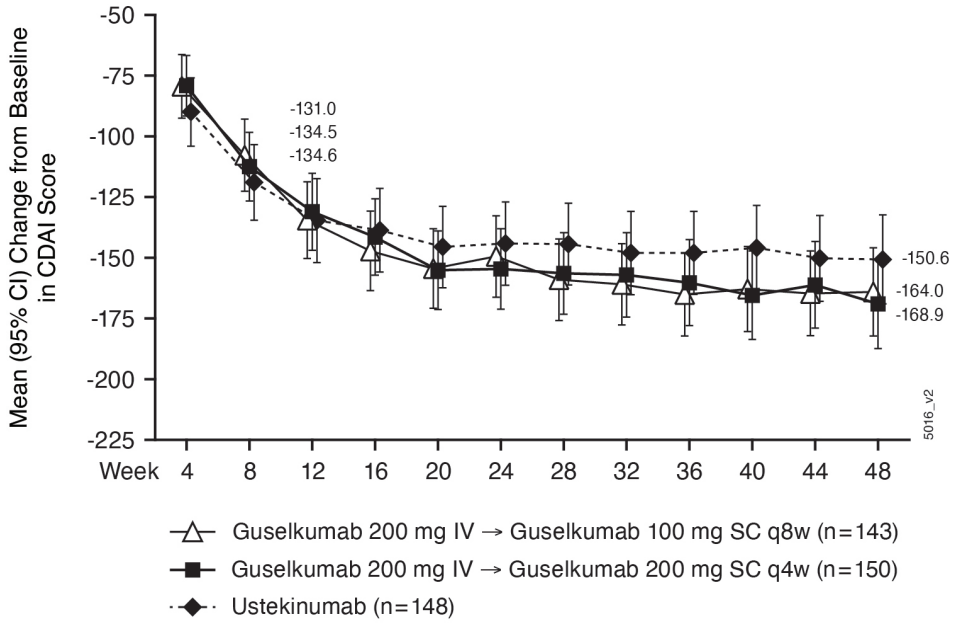
* significant p-values (relative to ustekinumab) based on the testing procedure; † nominal p<0.05

A subgroup analysis was also performed among those participants who had a baseline mean daily stool frequency score of at least 4 or abdominal pain score of at least 2. The proportion of participants in PRO-2 remission at Week 48 for the guselkumab 200 mg SC q4w treatment group (57.4%), the

guselkumab 100 mg SC q8w treatment group (54.3%), and the ustekinumab treatment group (54.3%) was similar to the main analysis.

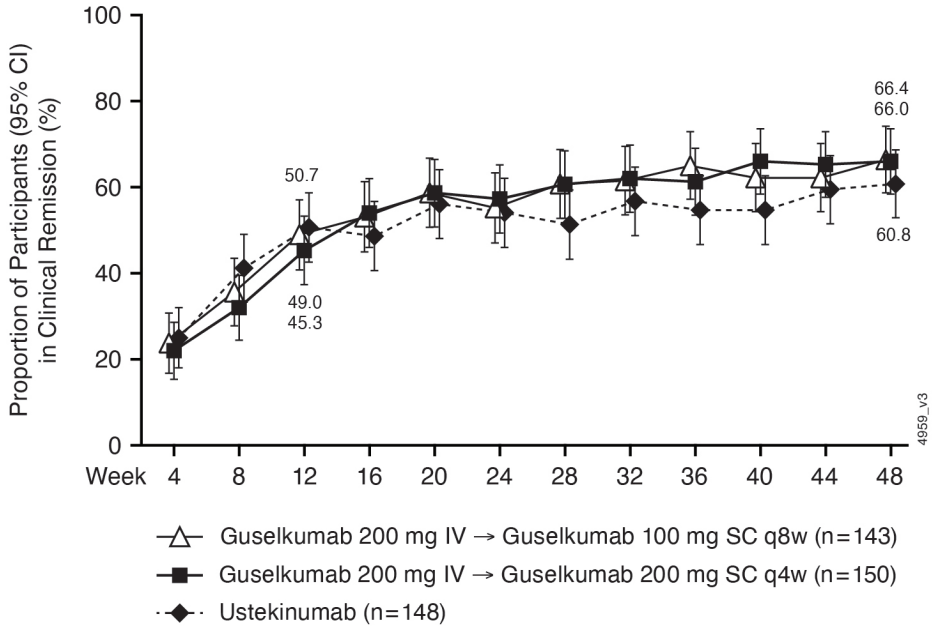
Other Efficacy Analyses

Figure 31: Line Plot of Mean (95% CI) for Change from Baseline in CDAI by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)



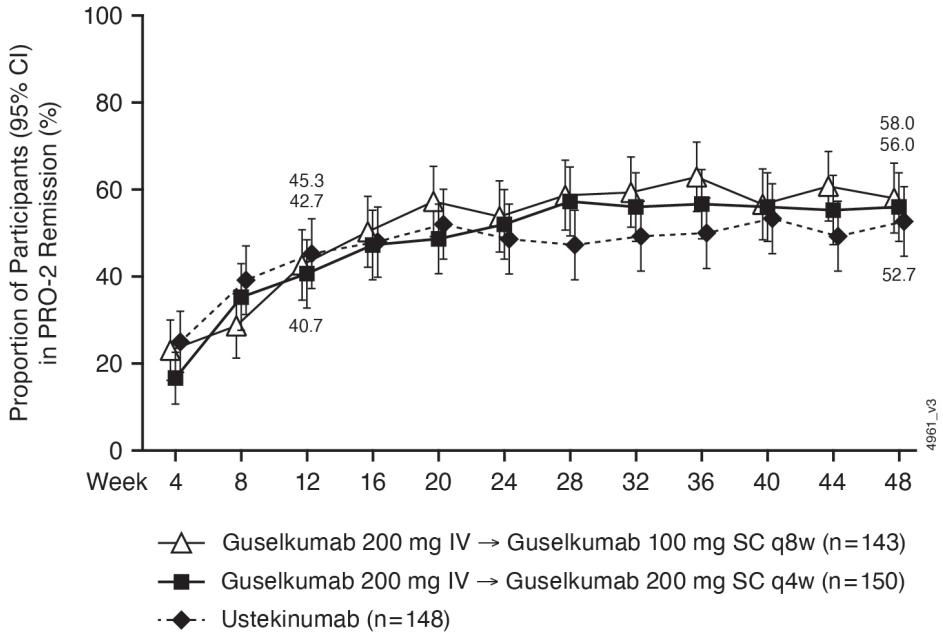
Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 32: Line Plot of Proportion of Subjects in Clinical Remission by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)



Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 33: Line Plot of Proportion of Participants in PRO-2 Remission by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)



Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

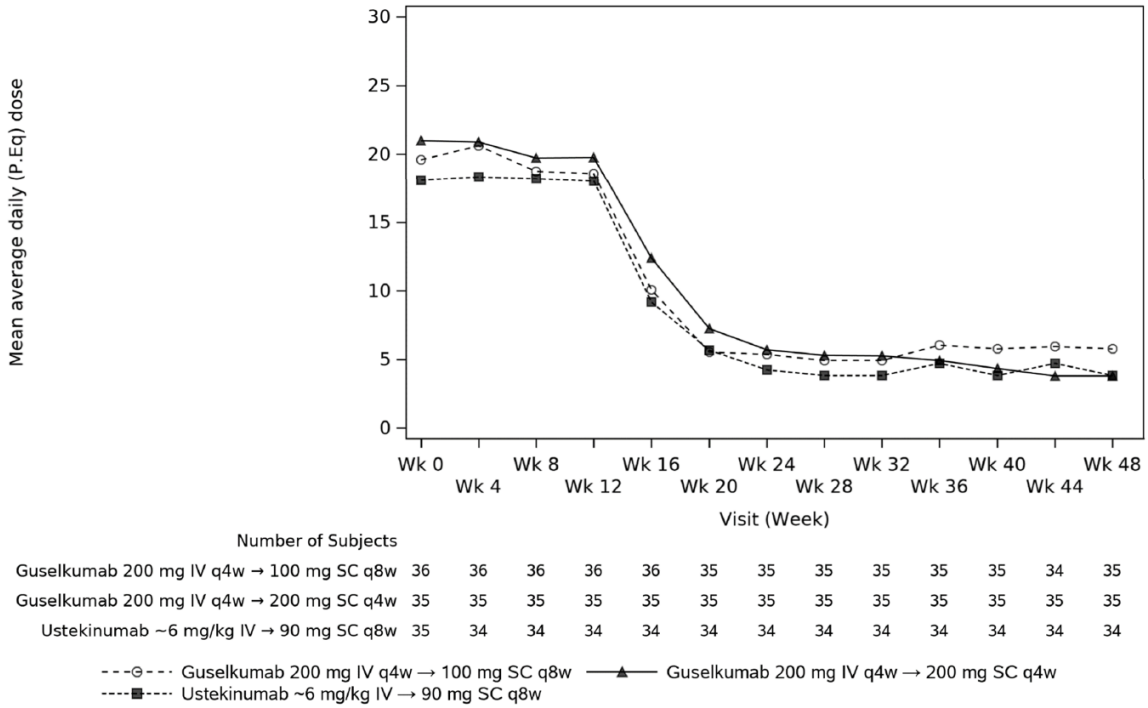
Corticosteroid-Related Endpoints through Week 48

Among participants who achieved the endpoint of clinical remission at Week 48, 97% were corticosteroid-free.

Over a third of the population was receiving corticosteroids at baseline. Among participants receiving corticosteroids at baseline, the proportions of participants who were able to eliminate corticosteroids at Week 48 were 66.7% in the guselkumab 200 mg SC q4w treatment group, 70.9% in the guselkumab 100 mg SC q8w treatment group, and 71.7% in the ustekinumab treatment group.

Additionally, among participants receiving corticosteroids at baseline, 58.8% of participants in the guselkumab 200 mg SC q4w treatment group, 52.7% of participants in the guselkumab 100 mg SC q8w treatment group, and 54.7% of participants in the ustekinumab treatment group achieved corticosteroid-free clinical remission at Week 48.

Figure 34: Average daily prednisone equivalent doses (excluding budesonide and beclomethasone dipropionate) by Visit through Week 48 Among Those Receiving Oral Corticosteroids other Than Budesonide or Beclomethasone Dipropionate at Baseline; Primary Analysis Set (GALAXI 3)



Inflammatory Biomarker Endpoints

Greater changes from baseline in inflammatory biomarkers (CRP and fecal calprotectin) were observed in the combined guselkumab 200 mg IV treatment group as early as Week 4 and continued to decrease through Week 12 as compared with the placebo treatment group. The change from baseline in the guselkumab treatment groups was maintained through Week 48.

Patient-reported Outcomes

Abdominal Pain

Among participants with baseline average daily abdominal pain scores >1 (based on CDAI), proportion of patients with average dailiy abdominal pain score ≤1:

- Week 12
    - combined guselkumab 200 mg IV group:53.4%
    - placebo group: 19.4%.
- Week 48

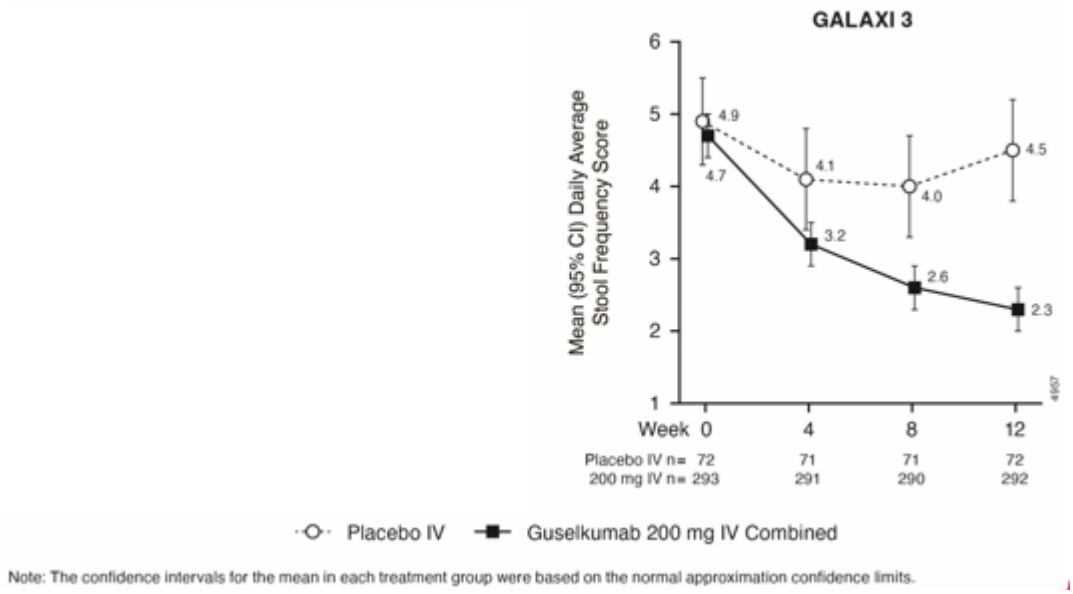
    - guselkumab 200 mg SC q4w group: 69.0% treatment group, in the
    - guselkumab 100 mg SC q8w group: 64.7%, and in the
    - ustekinumab group: 67.4%

Stool Frequency

Among participants with an average daily number of liquid or very soft stools >3 at baseline (based on CDAI) proportion of patients with average daily number of liquid or very soft stools ≤3:

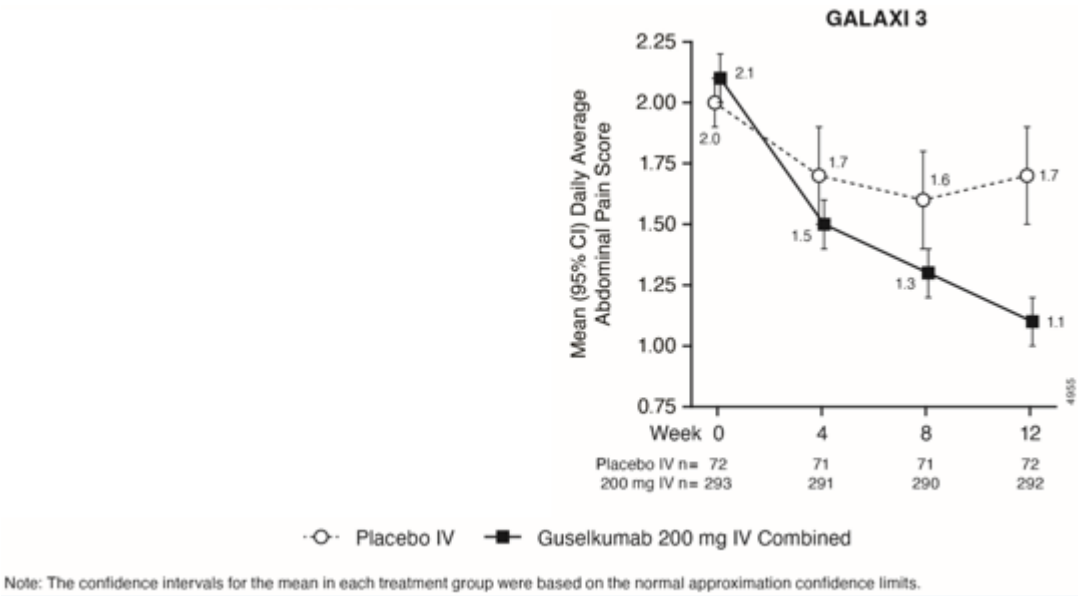
- Week 12
    - combined guselkumab 200 mg IV group: 56.9%
    - placebo group: 21.8%
- Week 48
    - guselkumab 200 mg SC q4w group: 61.7%
    - guselkumab 100 mg SC q8w group: 63.8%
    - ustekinumab group: 60.0%

Figure 35: Mean (95% CI) Daily Average Stool Frequency Through Week 12; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)



Note: The confidence intervals for the mean in each treatment group were based on the normal approximation confidence limits.

Figure 36: Mean (95% CI) Daily Average Abdominal Pain Score Through Week 12; Primary Analysis Set (CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



Note: The confidence intervals for the mean in each treatment group were based on the normal approximation confidence limits.

Fatigue

Table 41: Improvements in the PROMIS-Fatigue SF 7a T-scores

	Guselkumab			Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	
Week 12[a,b]				
N	140	147	287	141
Mean (SD)	-6.33 (7.949)	-5.96 (7.996)	-6.14 (7.962)	-5.38 (8.077)
Median	-5.60	-5.60	-5.60	-3.40
Range	(-29.2; 16.9)	(-27.5; 11.4)	(-29.2; 16.9)	(-37.5; 11.2)
IQ range	(-10.25; 0.00)	(-11.20; 0.00)	(-11.20; 0.00)	(-9.70; 0.00)
N[c]	141	147	288	143
LS Means (SE)[d]	-6.33 (0.623)	-5.86 (0.613)	-6.09 (0.442)	-5.75 (0.621)
LS Mean Difference (95% CI) from Ustekinumab[d]	0.58 (-1.13, 2.30)	0.11 (-1.58, 1.81)	0.34 (-1.13, 1.82)	
p-value[d]	0.504	0.897	0.649	
Week 48[a,b]				
N	139	144	283	139
Mean (SD)	-7.75 (8.507)	-7.08 (8.361)	-7.41 (8.425)	-7.02 (9.502)
Median	-6.90	-5.60	-6.60	-5.60
Range	(-34.4; 15.3)	(-31.5; 5.6)	(-34.4; 15.3)	(-38.4; 15.3)
IQ range	(-12.80; 0.00)	(-12.00; 0.00)	(-12.60; 0.00)	(-11.60; 0.00)
N[c]	141	147	288	143
LS Means (SE)[d]	-7.92 (0.688)	-6.91 (0.679)	-7.41 (0.488)	-7.35 (0.687)
LS Mean Difference (95% CI) from Ustekinumab[d]	0.57 (-1.33, 2.46)	-0.44 (-2.32, 1.44)	0.06 (-1.58, 1.69)	
p-value[d]	0.557	0.649	0.946	

Key: ICE=intercurrent event

a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint had their baseline value carried forward. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available.

b Missing data imputation: After accounting for ICE strategies, subjects who were missing PROMIS-29 score at the designated analysis timepoint did not have their missing data imputed.

c Number of subjects with baseline value and at least one post-baseline visit value.

d The LS Mean and SE for each treatment group, LS Mean difference between the treatment groups and p-values for the comparisons of each guselkumab treatment group with the ustekinumab group were based on MMRM analysis including change from baseline in PROMIS-29 score as the response; treatment group, visit, baseline PROMIS-29 score, BIO-Failure status (Yes, No), baseline CDAI score (.300 or >300), baseline SES-CD score (.12 or >12), baseline corticosteroid use (Yes or No), an interaction term of visit with treatment group and an interaction term of visit with baseline PROMIS-29 score as explanatory variables.

Improvement in Health-related Quality of Life

PROMIS-29

At Week 12, the combined guselkumab 200 mg IV treatment group had greater improvements from baseline in the mean scores for pain intensity NRS, physical and mental health summary (PCS and MCS), and each of the 7 PROMIS-29 domains (depression, an anxiety, fatigue, pain interference, physical function, sleep disturbance, ability to participate in social roles and activities) compared with the placebo treatment group.

At Week 48, the MAH considered that the proportions of participants who achieved improved PROMIS-29 scores were similar between the guselkumab treatment groups and the ustekinumab treatment group.

IBDQ

At Week 12, the combined guselkumab 200 mg IV treatment group (47.8%) had a numerically greater proportion of participants in IBDQ remission compared with the placebo treatment group (27.8%).

At Week 48, the proportions of participants in IBDQ remission were 51.3% in the guselkumab 200 mg SC q4w treatment group, 59.4% in the guselkumab 100 mg SC q8w treatment group, and 49.3% in the ustekinumab treatment group.

Table 42: Summary of Change From Baseline in IBDQ Total Score and Dimensions by Visit Through Week 48; Primary Analysis Set (CNTO1959CRD3001 GALAXI 3)

	Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Primary	143	150	293	148
IBDQ Total Score				
Baseline				
N	140	147	287	143
Mean (SD)	126.4 (31.72)	126.0 (28.21)	126.2 (29.92)	129.2 (31.43)
Median	127.5	125.0	127.0	129.0
Range	(49; 201)	(60; 188)	(49; 201)	(52; 201)
IQ range	(104.5; 148.5)	(109.0; 143.0)	(107.0; 146.0)	(107.0; 146.0)
Week 8[a,b]				
N	138	139	277	143
Mean (SD)	159.4 (35.26)	157.9 (31.23)	158.7 (33.25)	161.0 (31.16)
Median	162.5	161.0	162.0	164.0
Range	(77; 218)	(68; 209)	(68; 218)	(67; 220)
IQ range	(135.0; 186.0)	(134.0; 183.0)	(134.0; 186.0)	(141.0; 185.0)
Week 12[a,b]				
N	141	148	289	145
Mean (SD)	165.1 (37.80)	160.2 (35.63)	162.6 (36.72)	162.4 (36.45)
Median	174.0	164.0	167.0	166.0
Range	(69; 218)	(60; 216)	(60; 218)	(63; 218)
IQ range	(146.0; 195.0)	(137.0; 190.5)	(141.0; 193.0)	(144.0; 192.0)
Week 24[a,b]				
N	141	148	289	142
Mean (SD)	166.8 (39.76)	165.7 (37.36)	166.2 (38.48)	167.4 (34.15)
Median	180.0	177.0	179.0	172.0
Range	(56; 224)	(46; 221)	(46; 224)	(67; 220)
IQ range	(147.0; 197.0)	(143.5; 197.0)	(145.0; 197.0)	(144.0; 195.0)
Week 48[a,b]				
N	141	144	285	142
Mean (SD)	168.8 (41.16)	166.1 (37.53)	167.5 (39.32)	165.6 (35.99)
Median	183.0	174.5	179.0	170.5
Range	(51; 221)	(60; 224)	(51; 224)	(67; 222)

EQ-5D/EQ-VAS

Improvements observed in EQ-5D (pain/discomfort and usual activities) and EQ-VAS were greater in the combined guselkumab 200 mg IV treatment group at Week 12 compared with the placebo treatment group. At Week 48, numerically greater proportions of participants in both guselkumab treatment groups compared with the ustekinumab treatment group achieved improved status in the EQ-5D (dimensions of mobility and self-care) and EQ-VAS.

2.4.2.2. Study CRD3004 - GRAVITI study

GRAVITI study is an ongoing, Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in participants with moderately to severely active CD.

Methods

Study participants

The participants are adult patients with moderately to severely active CD (of at least 3 months' duration). Participants must have had colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy.

At baseline, participants had to have active CD, defined as clinically active CD with CDAI score ≥220 but ≤450 and either a mean daily stool frequency count ≥4, based on the unweighted CDAI component of the number of liquid or very soft stools or mean daily abdominal pain score ≥2, based on the unweighted CDAI component of abdominal pain.

Patients must also have endoscopic evidence of ileocolonic CD: an SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease), as assessed by central endoscopy reading at the screening endoscopy, based on the presence of ulceration in at least 1 of the 5 ileocolonic segments, resulting in the following specified ulceration component scores of a minimum score of 1 for the component of "size of ulcers" and a minimum score of 1 for the component of "ulcerated surface".

The participants must have shown an inadequate response to or intolerance of prior conventional therapy (ie, oral corticosteroids or immunomodulators [6-MP/AZA/MTX]) or biologic therapy (ie, TNF antagonists or vedolizumab).

Participants must not have had complications of CD, a current or suspected abscess, a draining (ie, functioning) stoma or ostomy, or previously received a biologic agent targeting IL-12/23 or IL-23.

Treatments

- Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 200 mg SC q4w through Week 24
- Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 100 mg SC q8w through Week 24
- Placebo SC q4w from Week 0 through Week 24 (see rescue criteria below)

All participants in the placebo group who met at least 1 of the rescue criteria at Week 12 and Week 16, as applicable, received rescue treatment, ie, guselkumab 400 mg SC at Weeks 16, 20, and 24, followed by guselkumab 100 mg SC q8w. Rescue criteria were based on meeting either 1) CDAI score >220 and a <70-point improvement from baseline in the CDAI score at both Week 12 and Week 16, or 2) an increase in SES-CD score by at least 50% from baseline at Week 12. To maintain the blind, participants randomized to guselkumab who met at least 1 of the rescue criteria continued their assigned treatment regimen and received blinded sham rescue matching placebo SC injection.

At Week 24, all participants entered the extension phase and received the same treatment regimen that they were receiving at Week 24.

Objectives

Primary Objective

- To evaluate the efficacy, including clinical remission and endoscopic response, of guselkumab SC induction.

Secondary Objectives

- To evaluate the efficacy of guselkumab SC across a range of outcome measures.
- To evaluate the safety of guselkumab SC.

Outcomes/endpoints

Co-Primary Endpoints

- Clinical remission (CDAI score <150) at Week 12
- Endoscopic response (≥50% improvement from baseline in SES-CD score) at Week 12

Secondary Endpoints

- Clinical remission at Week 24
- PRO-2 remission (an abdominal pain [AP] mean daily score ≤1 and stool frequency [SF] mean daily score ≤3 and no worsening of AP or SF from baseline) at Week 12
- Clinical response (decrease from baseline in CDAI ≥100 points or clinical remission) at Week 12

Sample size

The study target enrollment was 318 participants. Participants who had an inadequate response or an inability to tolerate biologic therapy (BIO-Failure) were to represent approximately 35% to 65% of the study population.

Randomisation

At Week 0, participants were randomly assigned to 1 of 3 intervention groups of Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 200 mg SC q4w through Week 24, Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 100 mg SC q8w through Week 24, and Placebo SC q4w from Week 0 through Week 24 in a 1:1:1 ratio. The randomization was balanced by using randomly permuted blocks and stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-Failure status (Yes or No) at baseline (Week 0). Allocation to treatment group was performed using a central randomization center by means of an IWRS.

Blinding (masking)

In GRAVITI, the blind was maintained through the Week 48 DBL except for the Week 24 DBL when a limited number of Applicant personnel was unblinded to summary level analyses and/or participant-level treatment assignment. A separate study team, who remained blinded to treatment assignment at the time of the Week 24 DBL, was put in place to manage the conduct of the study after the Week 24 DBL. The full Applicant unblinding occurred after the Week 48 DBL.

The GRAVITI study applied a double-dummy approach such that guselkumab injections always had a matching placebo, including the rescue treatment.

Statistical methods

Primary Analysis of Co-Primary Estimands

The co-primary endpoints (clinical remission at Week 12 and endoscopic response at Week 12) were analyzed based on their primary estimands, considering treatment groups (dose regimens), target population, variable (endpoint), intercurrent events (ICEs) and corresponding strategies), and population-level summary (difference in proportions).

ICEs and Corresponding Strategies

Intercurrent events

1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc)

2. A prohibited change in CD medication

3. Discontinuation of study intervention due to lack of efficacy or an adverse event (AE) of worsening of CD

4. Discontinuation of study intervention due to Coronavirus disease 2019 (COVID-19) related reasons (excluding COVID-19 infection) or regional crisis

5. Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4.

Corresponding strategies

Participants experiencing any ICEs in categories 1 to 3 and 5 prior to the Week 12 visit were considered to be nonresponders for the co-primary endpoints (ie, composite strategy). For participants experiencing ICE 4, any data observed after the associated ICE were used for the analysis, if available (ie, treatment policy strategy). After accounting for the ICE strategies, participants who had a missing CDAI score at Week 12 were considered not to have achieved clinical remission at Week 12 (ie, nonresponder imputation [NRI]) and participants who had the SES-CD score missing at Week 12 were considered not to have achieved the endpoint of endoscopic response at Week 12 (ie, NRI).

Testing procedures

For testing of the co-primary endpoints, the efficacy of the combined guselkumab treatment group versus the placebo group was compared using a 2-sided Mantel-Haenszel test at a significance level of 0.05 while adjusting for the stratification factors. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-Failure status (Yes or No). The 2 guselkumab treatment groups were combined for comparisons through Week 12 as they had received the same induction dose regimen up to Week 12.

Sensitivity and supplementary analyses of the co-primary endpoints were performed to examine the robustness of the primary analysis results. Subgroup analyses were performed to evaluate consistency of treatment effect over baseline demographics, baseline disease characteristics, and prior and baseline medication use.

Analyses of the Secondary Estimands

The secondary endpoints (clinical remission at Week 24, PRO-2 remission at Week 12, and clinical response at Week 12) were analyzed similarly to the co-primary endpoints. The same ICEs and corresponding strategies that were specified for the co-primary endpoints were used. In addition, for clinical remission at Week 24, participants who met rescue criteria (ICE 6) were considered not to have achieved the endpoint (ie, composite strategy).

Testing Procedure

Statistical testing was performed at a significance level of 0.05 (2-sided). The Type I error was controlled using a multiplicity-controlled testing procedure. The testing procedure began with a fixed-sequence testing procedure to control the overall Type 1 error rate at the 0.05 level across the co-primary and secondary endpoints. The endpoints were tested sequentially.

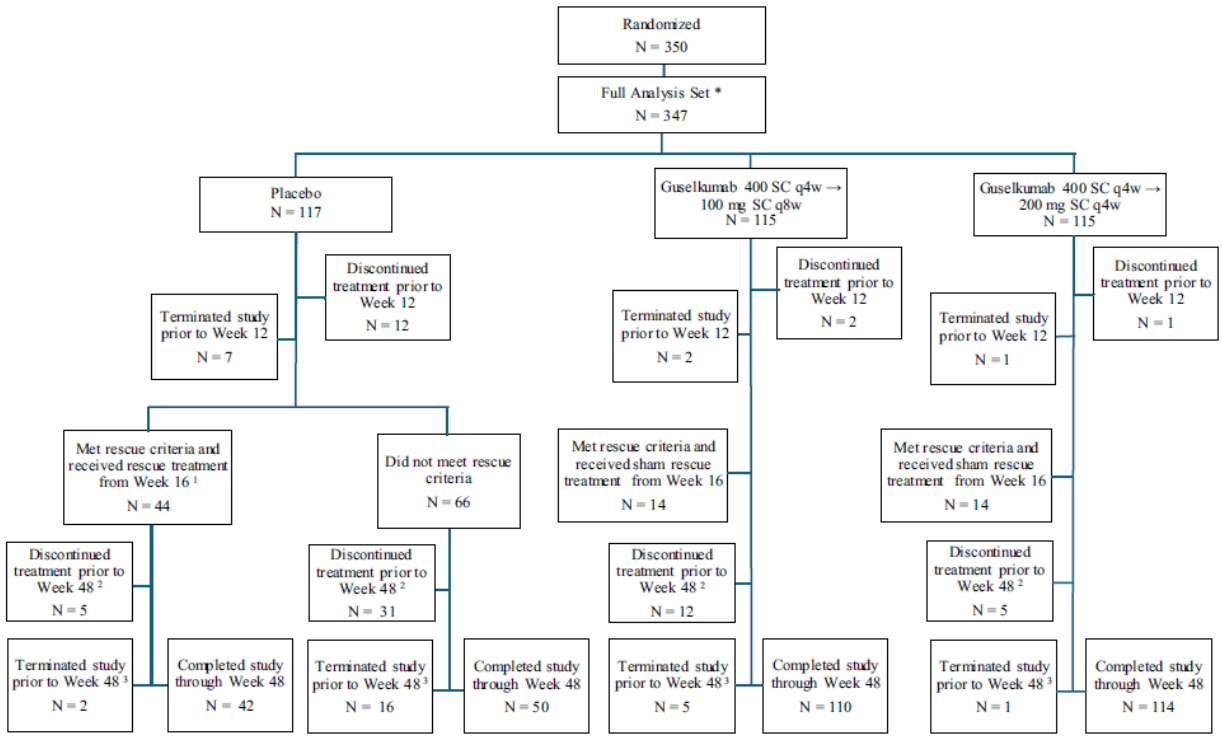
If any test in the sequence did not achieve significance at the 2-sided 0.05 level, the p-values for all of the subsequent tests were considered nominal.

Two exploratory endpoints (clinical remission at Week 48, endoscopic response at Week 48, for both dose groups) will be tested at the end of the fixed-sequence testing procedure; the testing of these endpoints will occur after the Week 48 database lock (DBL). Other exploratory endpoints were not multiplicity-controlled, and nominal p-values were presented.

Results

Participant flow

Figure 37: Disposition of All Randomized Participants Through Week 48 in CNTO1959CRD3004 (GRAVITI)



Recruitment

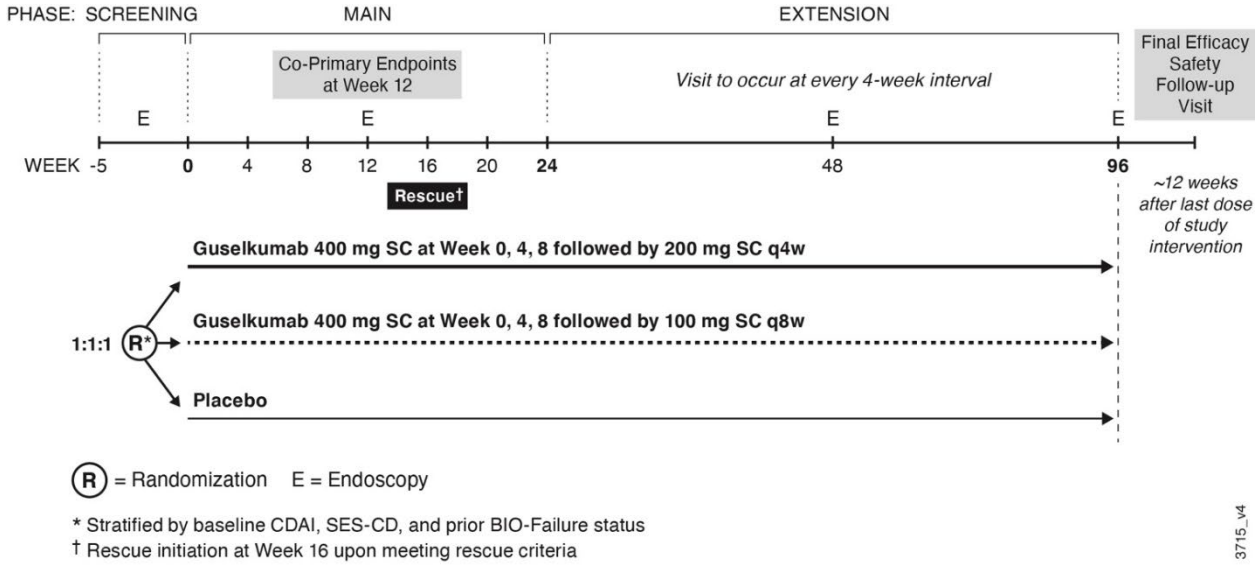
Study Initiation Date: 22 February 2022,

Data Cut-off Date: 01 March 2024

The study is ongoing.

Conduct of the study

Figure 38: Overview of the GRAVITI Study (CNTO1959CRD3004)



Baseline data

The main baseline demographic characteristics were:

Table 43: Summary of Main Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959CRD3004)

		Guselkumab			
	Placebo	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	Combined	Total
Analysis set: Full	117	115	115	230	347
Age, years					
N	117	115	115	230	347
Mean (SD)	36.0 (12.71)	37.4 (13.32)	39.1 (12.56)	38.2 (12.95)	37.5 (12.89)
Median	36.0	35.0	39.0	36.0	36.0
Range	(18; 72)	(18; 83)	(18; 67)	(18; 83)	(18; 83)
IQ range	(24.0; 42.0)	(27.0; 47.0)	(29.0; 47.0)	(28.0; 47.0)	(27.0; 45.0)
Sex					
N	117	115	115	230	347
Female	50 (42.7%)	49 (42.6%)	45 (39.1%)	94 (40.9%)	144 (41.5%)
Male	67 (57.3%)	66 (57.4%)	70 (60.9%)	136 (59.1%)	203 (58.5%)
Race					
N	117	115	115	230	347
American Indian or Alaska Native	0	0	0	0	0
Asian	28 (23.9%)	26 (22.6%)	22 (19.1%)	48 (20.9%)	76 (21.9%)
Black or African American	5 (4.3%)	0	4 (3.5%)	4 (1.7%)	9 (2.6%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	71 (60.7%)	79 (68.7%)	79 (68.7%)	158 (68.7%)	229 (66.0%)
Multiple[a]	0	0	0	0	0
Not Reported	13 (11.1%)	10 (8.7%)	10 (8.7%)	20 (8.7%)	33 (9.5%)

The baseline CD characteristics and history were generally balanced across the treatment groups and representative of a population with moderately to severely active CD. The median duration of CD was 8 years. At baseline, the median CDAI score was 289.0, the median SES-CD score was 10, the median fecal calprotectin was 643.0 mg/kg and the median CRP was 5.8 mg/L. Fecal calprotectin was >250 mg/kg at baseline for 71.7% of participants. CRP was >5 mg/L at baseline (defined as the reference range for the assay) for 54.8% of participants.

At baseline, 29.7% of participants were receiving oral corticosteroids (prednisone or its equivalent, budesonide, or beclomethasone), and 28.5% of participants were receiving immunomodulators (AZA,

6-MP, or MTX). The proportions of participants receiving these concomitant medications at baseline were similar among treatment groups.

A total of 46.4% of participants had a history of inadequate response or intolerance to previous biologic medication treatment (BIO-Failure subpopulation).

The remaining participants had a history of inadequate response to conventional therapy (CON-Failure subpopulation) (53.6%), without biologic failure. Within the CON-Failure population, 87% were naïve to biologic therapy (BIO-Naïve) and represented 46.4% of the overall population. 7.2% of the patients were biologic-experienced but not documented failure.

Efficacy Results (Guselkumab vs Placebo)

Table 44: Co-primary and Secondary Endpoints in GRAVITI; Full Analysis Set (CNTO1959CRD3004)

Week 12 Endpoints	Placebo (n=117)	Guselkumab 400 mg SC q4w (n=230)
Co-primary Endpoints		
Clinical remission at Week 12	25 (21.4%)	129 (56.1%)***
Adjusted treatment difference (95% CI)		34.9 (25.1, 44.6)
Endoscopic response at Week 12	25 (21.4%)	95 (41.3%)***
Adjusted treatment difference (95% CI)		19.9 (10.2, 29.6)
Week 12 Secondary Endpoints		
PRO-2 remission at Week 12	20 (17.1%)	113 (49.1%)
Adjusted treatment difference (95% CI)		32.1 (22.9, 41.2)***
Clinical response at Week 12	39 (33.3%)	169 (73.5%)
Adjusted treatment difference (95% CI)		40.3 (29.9, 50.7)***

		Guselkumab 400 mg SC q4w	
Week 24 Secondary Endpoint	**Placebo (n=117)**	**→ 100 mg SC q8w (n=115)**	**→ 200 mg SC q4w (n=115)**
Clinical remission at Week 24	25 (21.4%)	70 (60.9%)	67 (58.3%)
Adjusted treatment difference (95% CI)		39.3 (28.0, 50.7)***	37.0 (25.6, 48.4)***

*** p<0.001

The proportion of participants with ICEs prior to Week 12 were 3.5% in the combined guselkumab treatment group and 20.5% in the placebo group. After accounting for the ICE strategies, 1 participant (in placebo group) had missing response status related to CDAI and no missing endoscopic response status at Week 12.

The results from the prespecified sensitivity analyses of the co-primary endpoints were similar to the primary analyses.

All supplementary estimands and supportive analyses had similar results to the main analyses.

Subpopulation Analyses Based on CD-Related Medication

Greater proportions of participants who received guselkumab achieved all co-primary and secondary endpoints compared with the placebo treatment group across the predefined subpopulations including, BIO-Failure, CON-Failure, and BIO-Naïve subpopulations (a subset of the CON-Failure subpopulation).

Other Subgroup Analyses

Guselkumab was effective across all subpopulations evaluated (clinical remission at Week 12, endoscopic response at Week 12), and efficacy was not impacted by demographics, baseline disease characteristics, concomitant medications at baseline, or CD-related medical history.

Other Efficacy Analyses

Clinical Remission at Week 48

Table 45: Clinical Remission at Week 48; Full Analysis Set (Study CNTO1959CRD3004)

		Guselkumab		
	Placebo	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	Combined
Analysis set: Full analysis set	117	115	115	230
Week 48				
N	117	115	115	230
Subjects achieving clinical remission[a,b,c]	20 (17.1%)	69 (60.0%)	76 (66.1%)	145 (63.0%)
95% CI[d]	(10.3, 23.9)	(51.0, 69.0)	(57.4, 74.7)	(56.8, 69.3)
Adjusted treatment difference (95% CI)[e]		42.8 (31.6, 54.0)	48.9 (37.9, 59.9)	45.9 (36.6, 55.1)
p-value[e]		< 0.001	< 0.001	< 0.001

Key: ICE=intercurrent event, CD=Crohn´s disease, CDAI=Crohn´s Disease Activity Index, SES-CD=Simple Endoscopic Score for Crohn´s Disease

[a] Clinical remission is defined as CDAI score <150.

[b] Composite strategy: subjects who met ICE categories 1, 2, 3, 5, or 6 prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE 4 had their observed data used, if available.
ICE 1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.).
ICE 2. A prohibited change in CD medication.
ICE 3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening of CD.
ICE 4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis.
ICE 5. Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4.
ICE 6. Meet rescue criteria (only applicable after Week 16).

[c] After applying the ICE rules, subjects who had missing CDAI score at Week 48 were considered not to have achieved endpoint at Week 48.

[d] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.

[e] The adjusted treatment difference(s), confidence interval(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).

Endoscopic Response at Week 48

Table 46: Multiplicity-controlled Endpoint (Main Estimand, Composite and Treatment Policy): Endoscopic Response at Week 48; Full Analysis Set (Study CNTO1959CRD3004)

		Guselkumab		
	Placebo	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	Combined
Analysis set: Full analysis set	117	115	115	230
Week 48				
N	117	115	115	230
Subjects achieving endoscopic response[a,b,c]	8 (6.8%)	51 (44.3%)	59 (51.3%)	110 (47.8%)
95% CI[d]	(2.3, 11.4)	(35.3, 53.4)	(42.2, 60.4)	(41.4, 54.3)
Adjusted treatment difference (95% CI)[e]		37.5 (27.3, 47.7)	44.6 (34.1, 55.0)	40.9 (32.9, 48.9)
p-value[e]		< 0.001	< 0.001	< 0.001

Key: ICE=intercurrent event, CD=Crohn´s disease, CDAI=Crohn´s Disease Activity Index, SES-CD=Simple Endoscopic Score for Crohn´s Disease

[a] Endoscopic response is defined as ≥50% improvement from baseline in SES-CD score.

[b] Composite strategy: subjects who met ICE categories 1, 2, 3, 5, or 6 prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE 4 had their observed data used, if available.
ICE 1. A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.).
ICE 2. A prohibited change in CD medication.
ICE 3. Discontinuation of study intervention due to lack of efficacy or an AE of worsening of CD.
ICE 4. Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis.
ICE 5. Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4.
ICE 6. Meet rescue criteria (only applicable after Week 16).

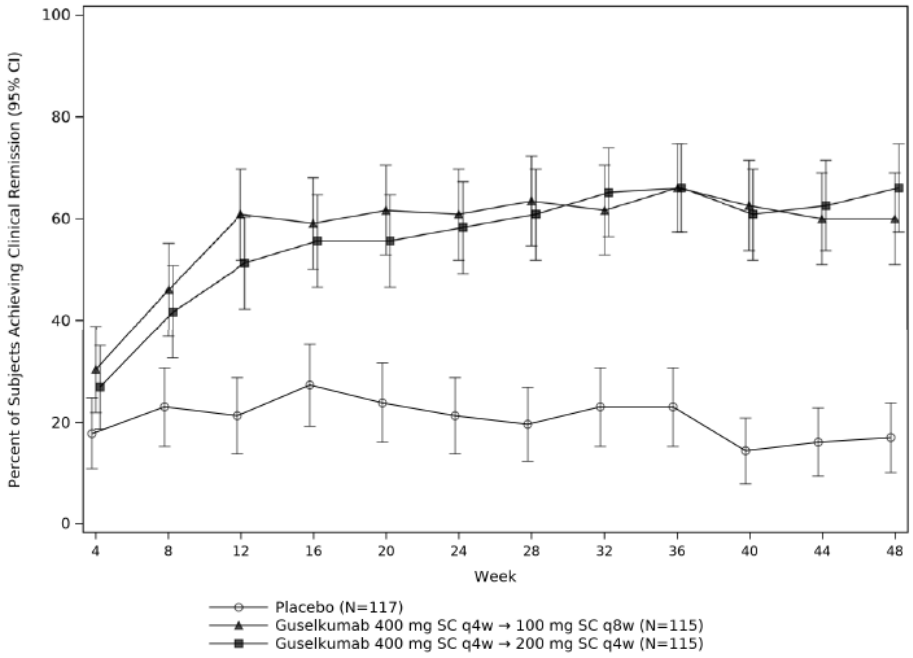
[c] After applying the ICE rules, subjects who had missing SES-CD score at Week 48 were considered not to have achieved endpoint at Week 48.

[d] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.

[e] The adjusted treatment difference(s), confidence interval(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).

CDAI

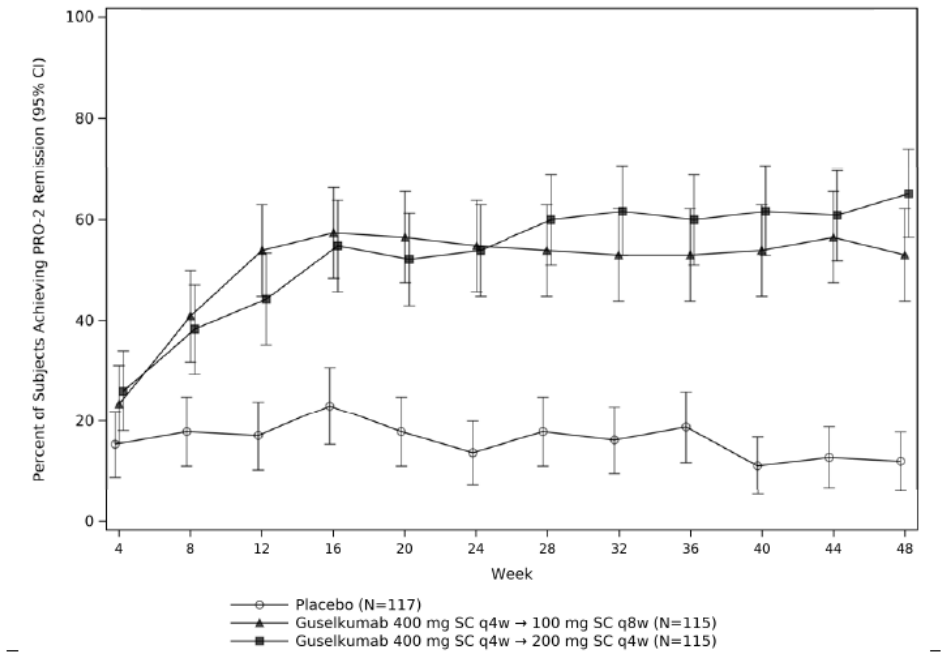
Figure 39: Line Plot of Clinical Remission Through Week 48; Full Analysis Set (Study CNTO1959CRD3004)



Key: ICE=intercurrent event, CD=Crohn´s disease, CDAI=Crohn´s Disease Activity Index, SES-CD=Simple Endoscopic Score for Crohn´s Disease

PRO-2

Figure 40: Line Plot of PRO-2 Remission Through Week 48; Full Analysis Set (Study CNTO1959CRD3004)



Key: ICE=intercurrent event, CD=Crohn´s disease, CDAI=Crohn´s Disease Activity Index, SES-CD=Simple Endoscopic Score for Crohn´s Disease

Corticosteroid-related Endpoints

The proportions of participants who were in corticosteroid-free clinical remission at Week 24 and Week 48 were greater in the guselkumab treatment groups (200 mg SC q4w [55.7%], 100 mg SC q8w [58.3%] at Week 24; and 200 mg SC q4w [65.2%], 100 mg SC q8w [58.3%] at Week 48) compared with 19.7% and 16.2% at Week 24 and Week 48, respectively in the placebo treatment group.

Among the 136 participants in both guselkumab treatment groups who achieved clinical remission at Week 24, 131 (96.3%) participants were corticosteroid-free. At baseline, the proportion of participants on corticosteroids were 33.0% in the guselkumab 200 mg SC q4w treatment group, 27.8% in the guselkumab 100 mg SC q8w treatment group, and 28.2% in the placebo treatment group. Among participants receiving corticosteroids at baseline, 76.3% in the guselkumab 200 mg SC q4w treatment group, 65.6% in the guselkumab 100 mg SC q8w treatment group, and 21.2% in the placebo treatment group were able to eliminate corticosteroids at Week 24. Among participants receiving corticosteroids at baseline, the proportion of participants achieving 90-day corticosteroid-free clinical remission was greater in the guselkumab treatment groups (71.1% in the 200 mg SC q4w treatment group and 46.9% in the 100 mg SC q8w treatment group) than in the placebo group (15.2%).

Among participants receiving corticosteroids at baseline, higher proportions of participants in the guselkumab treatment groups had completed corticosteroid tapering and were in corticosteroid-free clinical remission at Week 24 and Week 48 compared with the placebo group.

Inflammatory Biomarker Endpoints

Treatment with guselkumab resulted in reduction in markers of inflammation in the guselkumab treatment groups compared with the placebo group over time, starting at Week 4.

At baseline, 51.3% of participants in the 100 mg SC q8w treatment group, 53.0% in the 200 mg SC q4w treatment group, and 59.8% in the placebo treatment group had an elevated CRP (>5 mg/L) value. For those participants who had an elevated CRP level (>5 mg/L) at baseline, at Week 48, the proportion of participants who had achieved CRP levels ≤5 mg/L were 44.3%, 40.7%, and 2.9% in the guselkumab 200 mg SC q4w treatment group, 100 mg SC q8w treatment group, and placebo group, respectively.

At baseline, median FCP concentrations were similar across all treatment groups and ranged from 600.5 μg/g to 712 μg/g. Treatment with guselkumab reduced FCP levels over time starting from the Week 4 visit through Week 48. In the placebo group FCP levels remained around baseline levels through Week 48. The proportion of participants who had FCP >250 μg/g at baseline in the guselkumab 200 mg SC q4w, 100 mg SC q8w, and placebo groups were 69.3%, 72.2%, and 73.5%, respectively. Among these participants with elevated FCP levels (>250 μg/g) at baseline, a higher proportion of guselkumab-treated participants compared with placebo participants achieved FCP levels from Week 4 through Week 48 that were below cutoffs of ≤250 μg/g, ≤100 μg/g or ≤50 μg/g.

Fistula Response

Among participants who had open or draining fistulas at baseline, the proportions of participants who achieved fistula response at Week 48, were: 18.8% in the 200 mg SC q4w treatment group, 80.0% in the 100 mg SC q8w treatment group, and 7.1% in the placebo group. The interpretation of fistula response results is limited by the small size of the subgroup with at least 1 open or draining fistula at baseline.

Patient-Reported Outcomes and Health-related Quality of Life

Abdominal Pain

Among participants with baseline average daily abdominal pain scores >1 (based on CDAI), a numerically greater proportion of participants in the guselkumab 200 mg SC q4w treatment group

(67.6%) and guselkumab 100 mg SC q8w treatment group (59.1%) achieved an average daily abdominal pain score ≤1 compared with the placebo treatment group (15.9%) at Week 48.

Stool Frequency

Among participants with an average daily number of liquid or very soft stools >3 at baseline (based on CDAI), a numerically greater proportion of participants in the guselkumab 200 mg SC q4w treatment group (72.0%) and guselkumab 100 mg SC q8w treatment group (59.4%) had an average daily number of liquid or very soft stools ≤3 compared with the placebo treatment group (21.6%) at Week 48.

Fatigue

The PROMIS-Fatigue SF 7a was not used in GRAVITI.

At Week 12, the proportion of participants to achieve a ≥7-point improvement in the PROMIS-29 fatigue domain was 39.6% in the combined guselkumab 400 mg SC treatment group and 21.4% in the placebo treatment group. Treatment differences were also observed at Week 24 for both guselkumab treatment groups compared with the placebo treatment group.

At Week 12, the mean change from baseline for the fatigue domain of PROMIS-29 was greater in the combined guselkumab (400 mg SC) treatment group compared with the placebo treatment group. Improved mean changes from baseline were also observed at Week 24 for both guselkumab treatment groups compared with the placebo treatment group.

Improvement in Health-related Quality of Life

PROMIS-29

At Week 12, the combined guselkumab (400 mg SC) treatment group had greater improvements from baseline in the mean scores for pain intensity, NRS, physical and mental health summary (PCS and MCS), and 5 of the 7 PROMIS-29 domains (fatigue, pain interference, physical function, ability to participate in social roles and activities and sleep disturbance) compared with the placebo treatment group.

At Week 24 and Week 48, both guselkumab treatment groups had greater improvements from baseline in the mean scores for pain intensity NRS, physical and mental health summary (PCS and MCS), and the 7 PROMIS-29 domains (anxiety, depression, fatigue, pain interference, physical function, ability to participate in social roles and activities and sleep disturbance) compared with the placebo treatment group.

IBDQ

A numerically greater proportion of participants achieved IBDQ remission at Week 12 in the combined guselkumab (400 mg SC) treatment group (47.8%) compared with the placebo treatment group (23.1%). Greater proportions of participants achieving IBDQ remission were also observed at Week 24 and Week 48 for both guselkumab treatment groups compared with the placebo treatment group.

A greater mean change from baseline in IBDQ total score and each domain score at Week 12 was seen in the combined guselkumab (400 mg SC) treatment group compared with the placebo treatment group. Greater mean changes from baseline were also observed at Week 24 and Week 48 for both guselkumab treatment groups compared with the placebo treatment group.

Ancillary analyses

Subgroup analyses of the GALAXI 2 and GALAXI 3 studies on the subpopulations (BIO-Failure/CON-Failure/BIO-Naive) for co-primary endpoints and major secondary endpoints at Weeks 12 and 48 are provided in the tables below.

Table 47: Short-term co-Primary and key secondary endpoints by Biological failure status – GALAXI 2

	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	76	289
Subgroup: BIO-Failure	39	150
Clinical remission at Week 12[a,b]	9 (23.1%)	67 (44.7%)
Endoscopic response at Week 12[a,b]	2 (5.1%)	40 (26.7%)
PRO-2 remission at Week 12[a,b]	5 (12.8%)	61 (40.7%)
Fatigue response at Week 12[a,b]	10 (25.6%)	62 (41.3%)
Endoscopic remission at Week 12[a,b]	0	13 (8.7%)
Subgroup: CON-Failure	37	139
Clinical remission at Week 12[a,b]	8 (21.6%)	69 (49.6%)
Endoscopic response at Week 12[a,b]	6 (16.2%)	69 (49.6%)
PRO-2 remission at Week 12[a,b]	11 (29.7%)	63 (45.3%)
Fatigue response at Week 12[a,b]	12 (32.4%)	69 (49.6%)
Endoscopic remission at Week 12[a,b]	1 (2.7%)	30 (21.6%)
Subgroup: BIO-Naive	34	121
Clinical remission at Week 12[a,b]	6 (17.6%)	60 (49.6%)
Endoscopic response at Week 12[a,b]	5 (14.7%)	62 (51.2%)
PRO-2 remission at Week 12[a,b]	8 (23.5%)	52 (43.0%)
Fatigue response at Week 12[a,b]	11 (32.4%)	58 (47.9%)
Endoscopic remission at Week 12[a,b]	1 (2.9%)	27 (22.3%)

Clinical remission is defined as CDAI score <150.
Endoscopic response is defined as ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.
PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.
Fatigue response is defined as improvement of ≥7 points in PROMIS Fatigue Short Form 7a.
Endoscopic remission (region-specific definition) is defined as SES-CD Score ≤2.
a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12.
b Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI, SES-CD, PROMIS Fatigue 7a, SF or AP score at the designated analysis timepoint were considered not having achieved the endpoint at that timepoint.

Table 48: Long-term co-Primary and key secondary endpoints by Biological failure status – GALAXI 2

		Guselkumab	
	Placebo	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w
Analysis set: Primary	76	143	146
Subgroup: BIO-Failure	39	77	73
Corticosteroid-free clinical remission at Week 48[a,b]	5 (12.8%)	28 (36.4%)	37 (50.7%)
Endoscopic response at Week 48[a,b]	3 (7.7%)	27 (35.1%)	20 (27.4%)
Subgroup: CON-Failure	37	66	73
Corticosteroid-free clinical remission at Week 48[a,b]	4 (10.8%)	37 (56.1%)	38 (52.1%)
Endoscopic response at Week 48[a,b]	2 (5.4%)	28 (42.4%)	36 (49.3%)
Subgroup: BIO-Naive	34	58	63
Corticosteroid-free clinical remission at Week 48[a,b]	2 (5.9%)	32 (55.2%)	33 (52.4%)
Endoscopic response at Week 48[a,b]	2 (5.9%)	26 (44.8%)	30 (47.6%)

Corticosteroid-free clinical remission is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
Endoscopic response is defined as ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.

a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], were not in clinical response at Week 12 [ICE 6] or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 non-responder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 48.
b Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD score at Week 48 were considered not having achieved the endpoint at Week 48.

Table 49: Short-term co-Primary and key secondary endpoints by Biological failure status – GALAXI 3

		Guselkumab	
	Placebo	200 mg IV	Combined
Analysis set: Primary	72		293
Subgroup: BIO-Failure	39		150
Clinical remission at Week 12[a,b]	6 (15.4%)		71 (47.3%)
Endoscopic response at Week 12[a,b]	3 (7.7%)		47 (31.3%)
PRO-2 remission at Week 12[a,b]	5 (12.8%)		59 (39.3%)
Fatigue response at Week 12[a,b]	7 (17.9%)		64 (42.7%)
Endoscopic remission at Week 12[a,b]	0		14 (9.3%)
Subgroup: CON-Failure	33		143
Clinical remission at Week 12[a,b]	5 (15.2%)		67 (46.9%)
Endoscopic response at Week 12[a,b]	7 (21.2%)		59 (41.3%)
PRO-2 remission at Week 12[a,b]	5 (15.2%)		63 (44.1%)
Fatigue response at Week 12[a,b]	6 (18.2%)		63 (44.1%)
Endoscopic remission at Week 12[a,b]	6 (18.2%)		33 (23.1%)
Subgroup: BIO-Naive	27		123
Clinical remission at Week 12[a,b]	4 (14.8%)		61 (49.6%)
Endoscopic response at Week 12[a,b]	6 (22.2%)		51 (41.5%)
PRO-2 remission at Week 12[a,b]	4 (14.8%)		58 (47.2%)
Fatigue response at Week 12[a,b]	5 (18.5%)		56 (45.5%)
Endoscopic remission at Week 12[a,b]	5 (18.5%)		31 (25.2%)

Clinical remission is defined as CDAI score <150.
Endoscopic response is defined as ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.
PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.
Fatigue response is defined as improvement of ≥7 points in PROMIS Fatigue Short Form 7a.
Endoscopic remission (region-specific definition) is defined as SES-CD Score ≤2.
a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12.
b Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI, SES-CD, PROMIS Fatigue 7a, SF or AP score at the designated analysis timepoint were considered not having achieved the endpoint at that timepoint.

Table 50: Long-term co-Primary and key secondary endpoints by Biological failure status – GALAXI 3

		Guselkumab	
	Placebo	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w
Analysis set: Primary	72	143	150
Subgroup: BIO-Failure	39	76	74
Corticosteroid-free clinical remission at Week 48[a,b]	5 (12.8%)	37 (48.7%)	36 (48.6%)
Endoscopic response at Week 48[a,b]	2 (5.1%)	25 (32.9%)	27 (36.5%)
Subgroup: CON-Failure	33	67	76
Corticosteroid-free clinical remission at Week 48[a,b]	5 (15.2%)	26 (38.8%)	36 (47.4%)
Endoscopic response at Week 48[a,b]	2 (6.1%)	22 (32.8%)	27 (35.5%)
Subgroup: BIO-Naive	27	58	65
Corticosteroid-free clinical remission at Week 48[a,b]	5 (18.5%)	25 (43.1%)	32 (49.2%)
Endoscopic response at Week 48[a,b]	2 (7.4%)	22 (37.9%)	25 (38.5%)

Corticosteroid-free clinical remission is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
Endoscopic response is defined as ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.

a ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], were not in clinical response at Week 12 [ICE 6] or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 non-responder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-
19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 48.
b Missing d data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD score at Week 48 were considered not having achieved the endpoint at Week 48.

Other subgroup analyses

In GALAXI 2 and GALAXI 3 studies, guselkumab was effective across all subpopulations evaluated, and efficacy was not impacted by demographics, baseline disease characteristics, concomitant medications at baseline, or CD-related medical history.

Summary of main studies

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

Table 51: Summary of efficacy for trial CNTO1959CRD3001 (48-Week Clinical Study Report [GALAXI 2; Phase 3])

Title: **A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease**			
Study identifier	CNTO1959CRD3001		
Design	Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable ~4 years
Hypothesis	Superiority		
Treatments groups	Guselkumab 200 mg IV q4w → 200 mg SC q4w		Induction: 200 mg IV at Weeks 0, 4, 8; followed by Maintenance: 200 mg SC q4w (ie, at Weeks 12, 16, 20, 24, 28, 32, 36, 40, and 44).
	Guselkumab 200 mg IV q4w → 100 mg SC q8w		Induction: 200 mg IV at Weeks 0, 4, 8; followed by Maintenance: 100 mg SC q8w (ie, at Weeks 16, 24, 32, and 40).
	Guselkumab 200 mg IV combined		Combination of participants who received guselkumab 200 mg IV.
	Ustekinumab		Induction: ~6 mg/kg IV at Week 0; followed by Maintenance 90 mg SC q8w (ie, at weeks 8, 16, 24, 32, and 40).
	Placebo		Induction: IV at Week 0, Week 4, and Week 8 and Week 12 Maintenance: SC q4w from Week 8 through Week 44 for responders. Non-responders cross-over to ustekinumab at Week 12.
Endpoints and definitions	Co-Primary endpoints to evaluate guselkumab vs Placebo	Clinical remission at Week 12	CDAI <150
		Endoscopic response at Week 12	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2

	Major secondary (short-term) endpoints: evaluate guselkumab vs Placebo	PRO-2 remission at Week 12	AP mean daily score at or below 1 [AP≤1] and SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline
		Fatigue response at Week 12	An improvement of ≥7 points in PROMIS Fatigue Short Form 7a
		Endoscopic remission at Week 12	SES-CD score ≤2
	Major secondary (long-term) endpoints: evaluate guselkumab vs Placebo	Corticosteroid-free clinical remission at Week 48	CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48
		Endoscopic response at Week 48	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
	Major secondary (long-term) endpoints: evaluate guselkumab vs ustekinumab	Clinical remission at Week 48	CDAI <150
		Endoscopic response at Week 48	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
		Clinical remission at Week 48 and endoscopic response at Week 48	• CDAI <150 • ≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
		Endoscopic remission at Week 48	SES-CD score ≤2
		Corticosteroid-free clinical remission at Week 48	CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
		Durable clinical remission at Week 48	CDAI <150 for ≥80% of all visits between Week 12 and Week 48 [ie, at least 8 of 10 visits]), which must include Week 48.
		PRO-2 remission at Week 48	AP mean daily score at or below 1 [AP≤1] and SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline.
Database lock	20 October 2023 (date of last visit recorded as part of the database for this Week 48 CSR)		
Results and Analysis			
Analysis description	**Analysis of the Co-primary endpoint**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV combined	Placebo
	Number of Participants	289	76
	Number (%) of participants in clinical remission at Week 12	136 (47.1%)	17 (22.4%)
Effect estimates per comparison	Co-primary endpoint: Clinical remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	25.1 (14.1, 36.2)
		P-value	<0.001
Analysis description	**Analysis of the Co-primary endpoint**		

Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV combined	Placebo
	Number (%) of participants in endoscopic response at Week 12	109 (37.7%)	8 (10.5%)
Effect estimates per comparison	Co-primary endpoint: Endoscopic response at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	27.7 (19.3, 36.1)
		P-value	<0.001
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV Combined	Placebo
	Number of Participants	289	76
	Number (%) of participants in PRO-2 remission at Week 12	124 (42.9%)	16 (21.1%)
Effect estimates per comparison	Major Secondary Analysis: PRO-2 Remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	21.9 (11.3, 32.5)
		P-value	<0.001
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV Combined	Placebo
	Number (%) of participants in fatigue response Week 12	131 (45.3%)	22 (28.9%)
Effect estimates per comparison	Major Secondary Analysis: Fatigue Response at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	16.3 (4.6, 28.1)
		P-value	0.006
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
	Treatment group	Guselkumab 200 mg IV Combined	Placebo

Descriptive statistics and estimate variability	Number (%) of participants in endoscopic remission at Week 12	43 (14.9%)	1 (1.3%)	
Effect estimates per comparison	Major Secondary Analysis: Endoscopic Remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo	
		Adjusted treatment difference (95% CI)	13.7 (8.9, 18.6)	
		P-value	<0.001	
Analysis description	**Summary of the Major Secondary Endpoints with Long-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Placebo
	Number of Participants	146	143	76
	Number (%) of participants in corticosteroid-free clinical remission at Week 48	75 (51.4%)	65 (45.5%)	9 (11.8%)
Effect estimates per comparison	Major Secondary endpoint: Corticosteroid-free clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Placebo	
		Adjusted treatment difference (95% CI)	39.2 (28.1, 50.2)	
		P-value	<0.001	
		Comparison groups	Guselkumab 100 mg SC q8w vs Placebo	
		Adjusted treatment difference (95% CI)	34.9 (24.3, 45.5)	
		P-value	<0.001	
Analysis description	**Summary of the Major Secondary Endpoints with Long-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Placebo
	Number (%) of participants in endoscopic response at Week 48	56 (38.4%)	55 (38.5%)	5 (6.6%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Placebo	
		Adjusted treatment difference (95% CI)	31.5 (21.6, 41.4)	
		P-value	<0.001	
		Comparison groups	Guselkumab 100 mg SC q8w vs Placebo	
		Adjusted treatment difference (95% CI)	31.6 (21.8, 41.3)	
		P-value	<0.001	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			

Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number of Participants	146	143	143
	Number (%) of participants in clinical remission at Week 48 and endoscopic response at Week 48	72 (49.3%)	60 (42.0%)	56 (39.2%)
Effect estimates per comparison	Major Secondary endpoint: Clinical remission at Week 48 and endoscopic response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	10.2 (-0.6, 21.0)	
		P-value	0.065	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	2.8 (-8.4, 14.1)	
		P-value	0.620	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in endoscopic remission at Week 48	35 (24.0%)	38 (26.6%)	29 (20.3%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	3.8 (-5.2, 12.8)	
		P-value	0.407	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	6.4 (-3.4, 16.2)	
		P-value	0.199	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in clinical remission at Week 48	109 (74.7%)	92 (64.3%)	93 (65.0%)

Effect estimates per comparison	Major Secondary endpoint: Clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	9.5 (-0.7, 19.8)	
		P-value	0.069	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	-0.6 (-11.6, 10.5)	
		P-value	0.920	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in endoscopic response at Week 48	82 (56.2%)	70 (49.0%)	60 (42.0%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic Response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	14.5 (3.6, 25.4)	
		P-value	0.009	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	7.0 (-4.4, 18.3)	
		P-value	0.230	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in PRO-2 remission at Week 48	101 (69.2%)	86 (60.1%)	85 (59.4%)
Effect estimates per comparison	Major Secondary endpoint: PRO-2 remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	10.2 (-0.4, 20.8)	
		P-value	0.060	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	0.9 (-10.4, 12.2)	
		P-value	0.874	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			

Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in corticosteroid-free clinical remission at Week 48	104 (71.2%)	90 (62.9%)	87 (60.8%)
Effect estimates per comparison	Major Secondary endpoint: Corticosteroid-free clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	9.9 (-0.7, 20.6)	
		P-value	0.067	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	2.0 (-8.8, 12.9)	
		P-value	0.713	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in durable clinical remission at Week 48	76 (52.1%)	66 (46.2%)	64 (44.8%)
Effect estimates per comparison	Major Secondary endpoint: Durable clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	7.8 (-3.5, 19.2)	
		P-value	0.177	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	1.4 (-9.9, 12.7)	
		P-value	0.804	

Table 52: Summary of efficacy for trial CNTO1959CRD3001 (48-Week Clinical Study Report [GALAXI 3; Phase 3])

Title: **A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease**		
Study identifier	CNTO1959CRD3001	
Design	Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable ~4 years
Hypothesis	Superiority	

Treatments groups	Guselkumab 200 mg IV q4w → 200 mg SC q4w		Induction: 200 mg IV at weeks 0, 4, 8; followed by Maintenance: 200 mg SC q4w (ie, at weeks 12, 16, 20, 24, 28, 32, 36, 40, and 44).
	Guselkumab 200 mg IV q4w → 100 mg SC q8w		Induction: 200 mg IV at weeks 0, 4, 8; followed by Maintenance: 100 mg SC q8w (ie, at weeks 16, 24, 32, and 40).
	Guselkumab 200 mg IV combined		Combination of participants who received guselkumab 200 mg IV.
	Ustekinumab		Induction: ~6 mg/kg IV at Week 0; followed by Maintenance 90 mg SC q8w (ie, at weeks 8, 16, 24, 32, and 40).
	Placebo		Induction: IV at Week 0, Week 4, and Week 8 and Week 12 Maintenance: SC q4w from Week 8 through Week 44 for responders. Non-responders cross-over to ustekinumab at Week 12.
Endpoints and definitions	Co-Primary endpoints to evaluate guselkumab vs Placebo	Clinical remission at Week 12	CDAI <150
		Endoscopic response at Week 12	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
	Major secondary (short-term) endpoints: evaluate guselkumab vs Placebo	PRO-2 remission at Week 12	AP mean daily score at or below 1 [AP≤1] and SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline
		Fatigue response at Week 12	An improvement of ≥7 points in PROMIS Fatigue Short Form 7a
		Endoscopic remission at Week 12	SES-CD score ≤2
	Major secondary (long-term) endpoints: evaluate guselkumab vs Placebo	Corticosteroid-free clinical remission at Week 48	CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48
		Endoscopic response at Week 48	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
	Major secondary (long-term) endpoints: evaluate guselkumab vs ustekinumab	Clinical remission at Week 48	CDAI <150
		Endoscopic response at Week 48	≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
		Clinical remission at Week 48 and endoscopic response at Week 48	• CDAI <150 • ≥50% improvement from baseline in the SES-CD or SES-CD score ≤2
		Endoscopic remission at Week 48	SES-CD score ≤2
		Corticosteroid-free clinical remission at Week 48	CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
		Durable clinical remission at Week 48	CDAI <150 for ≥80% of all visits between Week 12 and Week 48 [ie, at least 8 of 10 visits]), which must include Week 48.

		PRO-2 remission at Week 48	AP mean daily score at or below 1 [AP≤1] and SF mean daily score at or below 3 [SF≤3], and no worsening of AP or SF from baseline.
Database lock	16 October 2023 (date of last visit recorded as part of the database for this Week 48 CSR)		
Results and Analysis			
Analysis description	**Analysis of the Co-primary endpoint**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV combined	Placebo
	Number of Participants	293	72
	Number (%) of participants in clinical remission at Week 12	138 (47.1%)	11 (15.3%)
Effect estimates per comparison	Co-primary endpoint: Clinical remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	31.2 (21.1, 41.3)
		P-value	<0.001
Analysis description	**Analysis of the Co-primary endpoint**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV combined	Placebo
	Number (%) of participants in endoscopic response at Week 12	106 (36.2%)	10 (13.9%)
Effect estimates per comparison	Co-primary endpoint: Endoscopic response at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	22.1 (12.2, 31.9)
		P-value	<0.001
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**		
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV Combined	Placebo
	Number of Participants	293	72
	Number (%) of participants in PRO-2 remission at Week 12	122 (41.6%)	10 (13.9%)
Effect estimates per comparison	Major Secondary Analysis: PRO-2 Remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo
		Adjusted treatment difference (95% CI)	27.2 (17.3, 37.1)

		P-value	<0.001	
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV Combined	Placebo	
	Number (%) of participants in fatigue response Week 12	127 (43.3%)	13 (18.1%)	
Effect estimates per comparison	Major Secondary Analysis: Fatigue Response at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo	
		Adjusted treatment difference (95% CI)	25.7 (15.2, 36.2)	
		P-value	<0.001	
Analysis description	**Major Secondary Endpoints with Short-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV Combined	Placebo	
	Number (%) of participants in endoscopic remission at Week 12	47 (16.0%)	6 (8.3%)	
Effect estimates per comparison	Major Secondary Analysis: Endoscopic Remission at Week 12	Comparison groups	Guselkumab 200 mg IV combined vs Placebo	
		Adjusted treatment difference (95% CI)	7.4 (-0.1, 14.9)	
		P-value	0.054	
Analysis description	**Summary of the Major Secondary Endpoints with Long-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Placebo
	Number of Participants	150	143	72
	Number (%) of participants in corticosteroid-free clinical remission at Week 48	72 (48.0%)	63 (44.1%)	10 (13.9%)
Effect estimates per comparison	Major Secondary endpoint: Corticosteroid-free clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Placebo	
		Adjusted treatment difference (95% CI)	33.5 (21.7, 45.2)	
		P-value	<0.001	
		Comparison groups	Guselkumab 100 mg SC q8w vs Placebo	
		Adjusted treatment difference (95% CI)	29.7 (18.5, 41.0)	
		P-value	<0.001	

Analysis description	**Summary of the Major Secondary Endpoints with Long-term Placebo-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Placebo
	Number (%) of participants in endoscopic response at Week 48	54 (36.0%)	47 (32.9%)	4 (5.6%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Placebo	
		Adjusted treatment difference (95% CI)	30.8 (21.3, 40.3)	
		P-value	<0.001	
		Comparison groups	Guselkumab 100 mg SC q8w vs Placebo	
		Adjusted treatment difference (95% CI)	27.1 (18.0, 36.3)	
		P-value	<0.001	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number of Participants	150	143	148
	Number (%) of participants in clinical remission at Week 48 and endoscopic response at Week 48	68 (45.3%)	59 (41.3%)	42 (28.4%)
Effect estimates per comparison	Major Secondary endpoint: Clinical remission and endoscopic response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	16.9 (5.8, 27.9)	
		P-value	0.003	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	12.7 (1.7, 23.7)	
		P-value	0.024	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w

	Number (%) of participants in endoscopic remission at Week 48	28 (18.7%)	34 (23.8%)	19 (12.8%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	5.3 (-2.8, 13.4)	
		P-value	0.203	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	10.9 (2.1, 19.7)	
		P-value	0.015	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in clinical remission at Week 48	99 (66.0%)	95 (66.4%)	90 (60.8%)
Effect estimates per comparison	Major Secondary endpoint: Clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w Ustekinumab	
		Adjusted treatment difference (95% CI)	5.0 (-6.1, 16.1)	
		P-value	0.378	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	5.6 (-5.2, 16.5)	
		P-value	0.308	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in endoscopic response at Week 48	74 (49.3%)	67 (46.9%)	48 (32.4%)
Effect estimates per comparison	Major Secondary endpoint: Endoscopic Response at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	16.8 (5.7, 28.0)	
		P-value	0.003	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	14.1 (2.9, 25.2)	
		P-value	0.013	

Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in PRO-2 remission at Week 48	84 (56.0%)	83 (58.0%)	78 (52.7%)
Effect estimates per comparison	Major Secondary endpoint: PRO-2 remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	3.0 (-8.4, 14.3)	
		P-value	0.609	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	5.3 (-5.9, 16.6)	
		P-value	0.351	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in corticosteroid-free clinical remission at Week 48	96 (64.0%)	92 (64.3%)	87 (58.8%)
Effect estimates per comparison	Major Secondary endpoint: Corticosteroid-free clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	4.9 (-6.3, 16.0)	
		P-value	0.390	
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab	
		Adjusted treatment difference (95% CI)	5.6 (-5.3, 16.5)	
		P-value	0.316	
Analysis description	**Major Secondary Endpoints with Long-term Ustekinumab-based Comparisons**			
Analysis population and time point description	Efficacy Analysis Set (Primary Analysis Set): All randomized participants who received at least 1 (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]).			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV q4w → 100 mg SC q8w	Ustekinumab ~6mg/kg IV → 90 mg SC q8w
	Number (%) of participants in durable clinical remission at Week 48	73 (48.7%)	72 (50.3%)	58 (39.2%)

Effect estimates per comparison	Major Secondary endpoint: Durable clinical remission at Week 48	Comparison groups	Guselkumab 200 mg SC q4w vs Ustekinumab
		Adjusted treatment difference (95% CI)	9.4 (-2.1, 20.8)
		P-value	0.108
		Comparison groups	Guselkumab 100 mg SC q8w vs Ustekinumab
		Adjusted treatment difference (95% CI)	11.2 (-0.1, 22.6)
		P-value	0.052

Table 53: Summary of efficacy for trial CNTO1959CRD3004 (48-Week Clinical Study Report [GRAVITI; Phase 3])

Title: **A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Crohn's Disease**			
Study identifier	CNTO1959CRD3004		
Design	Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable Ongoing; 72 weeks
Hypothesis	Superiority		
Treatments groups	Guselkumab 400 mg SC q4w → 200 mg SC q4w		Induction: 400 mg SC at weeks 0, 4, and 8 followed by guselkumab 200 mg SC every 4 weeks (q4w).
	Guselkumab 400 mg SC q4w → 100 mg SC q8w		Induction: 400 mg SC at weeks 0, 4, and 8 followed by guselkumab 100 mg SC every 8 weeks (q8w).
	Guselkumab 400 mg SC q4w combined		Combination of participants who received guselkumab 400 mg SC.
	Placebo		Induction: SC at Week 0, Week 4, and Week 8; followed by Maintenance: SC q4w. Participants who met the rescue criteria at Week 16 received guselkumab.
Endpoints and definitions	Co-primary endpoints	Clinical remission at Week 12	CDAI score <150
		Endoscopic response at Week 12	≥50% improvement from baseline in the SES-CD score
	Secondary endpoints	Clinical remission at Week 24	CDAI score <150
		PRO-2 remission at Week 12	An AP mean daily score ≤1 and SF mean daily score ≤3, and no worsening of AP or SF from baseline
		Clinical response at Week 12	Decrease from baseline in CDAI ≥100 points or clinical remission
Database lock	01 March 2024 (date of last observation from the last participant in the Week 48 database lock)		
Results and Analysis			
Analysis description	**Co-primary Analysis**		

Analysis population and time point description	Full Analysis Set: 347 randomized participants who received at least 1 dose of study intervention.			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 400 mg SC q4w	Placebo	
	Number of Participants	230	117	
	Number (%) of participants in clinical remission at Week 12	129 (56.1%)	25 (21.4%)	
Effect estimates per comparison	Co-primary endpoint: Clinical remission at Week 12	Comparison groups	Guselkumab 400 mg SC combined vs Placebo	
		Adjusted treatment difference (95% CI)	34.9 (25.1, 44.6)	
		P-value	<0.001	
Analysis description	**Co-primary Analysis**			
Analysis population and time point description	Full Analysis Set: 347 randomized participants who received at least 1 dose of study intervention			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 400 mg SC q4w	Placebo	
	Number (%) of participants in endoscopic response at Week 12	95 (41.3%)	25 (21.4%)	
Effect estimates per comparison	Co-primary endpoint: Endoscopic response at Week 12	Comparison groups	Guselkumab 400 mg SC combined vs Placebo	
		Adjusted treatment difference (95% CI)	19.9 (10.2, 29.6)	
		P-value	<0.001	
Analysis description	**Secondary Endpoints**			
Analysis population and time point description	Full Analysis Set: 347 randomized participants who received at least 1 dose of study intervention			
Descriptive statistics and estimate variability	Treatment group	Guselkumab 400 mg SC q4w → 200 mg SC q4w	Guselkumab 400 mg SC q4w → 100 mg SC q8w	Placebo
	Number of Participants	115	115	117
	Number (%) of participants in clinical remission at Week 24	67 (58.3%)	70 (60.9%)	25 (21.4%)
Effect estimates per comparison	Secondary Analysis: Clinical Remission at Week 24	Comparison groups	Guselkumab 200 mg SC q4w vs Placebo	
		Adjusted treatment difference (95% CI)	37.0 (25.6, 48.4)	
		P-value	<0.001	
		Comparison groups	Guselkumab 100 mg SC q8w vs Placebo	
		Adjusted treatment difference (95% CI)	38.5 (27.0, 49.9)	
		P-value	<0.001	
Analysis description	**Secondary Endpoints**			

Analysis population and time point description	Full Analysis Set: 347 randomized participants who received at least 1 dose of study intervention		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 400 mg SC q4w combined	Placebo
	Number of Participants	230	117
	Number (%) of participants in PRO-2 remission at Week 12	113 (49.1%)	20 (17.1%)
Effect estimates per comparison	Secondary Analysis: PRO-2 remission at Week 12	Comparison groups	Guselkumab 400 mg SC combined vs Placebo
		Adjusted treatment difference (95% CI)	32.1 (22.9, 41.2)
		P-value	<0.001
Analysis description	**Secondary Endpoints**		
Analysis population and time point description	Full Analysis Set: 347 randomized participants who received at least 1 dose of study intervention		
Descriptive statistics and estimate variability	Treatment group	Guselkumab 400 mg SC q4w combined	Placebo
	Number of Participants	230	117
	Number (%) of participants in clinical response at Week 12	169 (73.5%)	39 (33.3%)
Effect estimates per comparison	Secondary Analysis: Clinical Response at Week 12	Comparison groups	Guselkumab 400 mg SC combined vs Placebo
		Adjusted treatment difference (95% CI)	40.3 (29.9, 50.7)
		P-value	<0.001

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

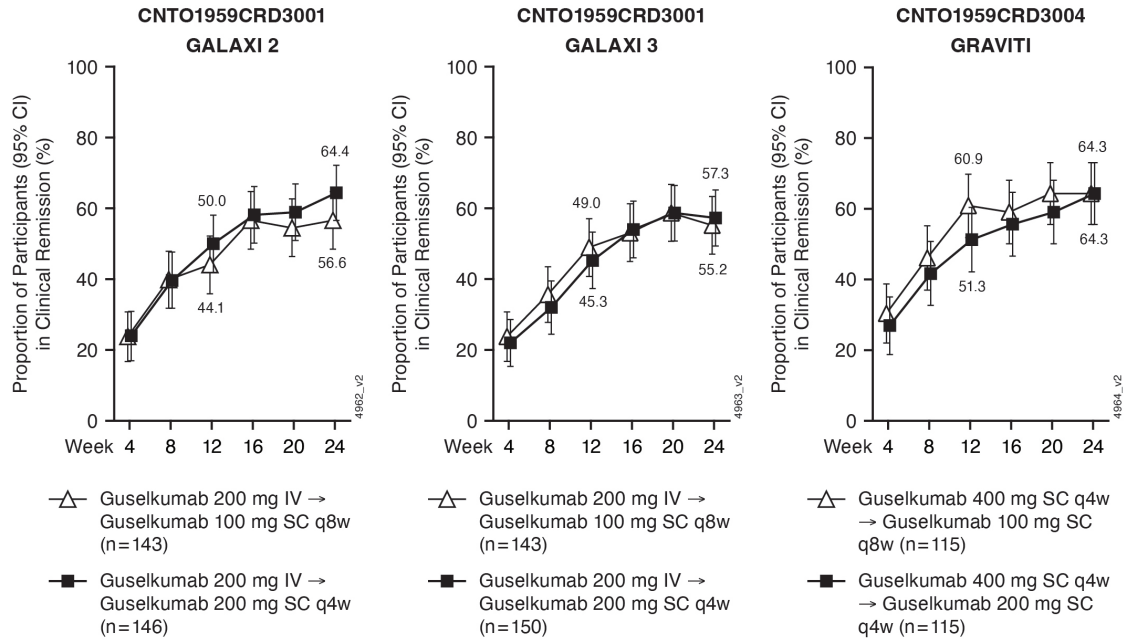
Cross study comparison – GALAXI 2, GALAXI 3 and GRAVITI studies

GALAXI and GRAVITI studies

The GALAXI and GRAVITI cross-study comparisons are aimed at characterizing the SC induction relative to IV induction. Week 12 efficacy results have been presented previously for the individual studies. The comparison hereafter focuses at Week 24, which is the timepoint at which there is maintenance data for the GRAVITI study.

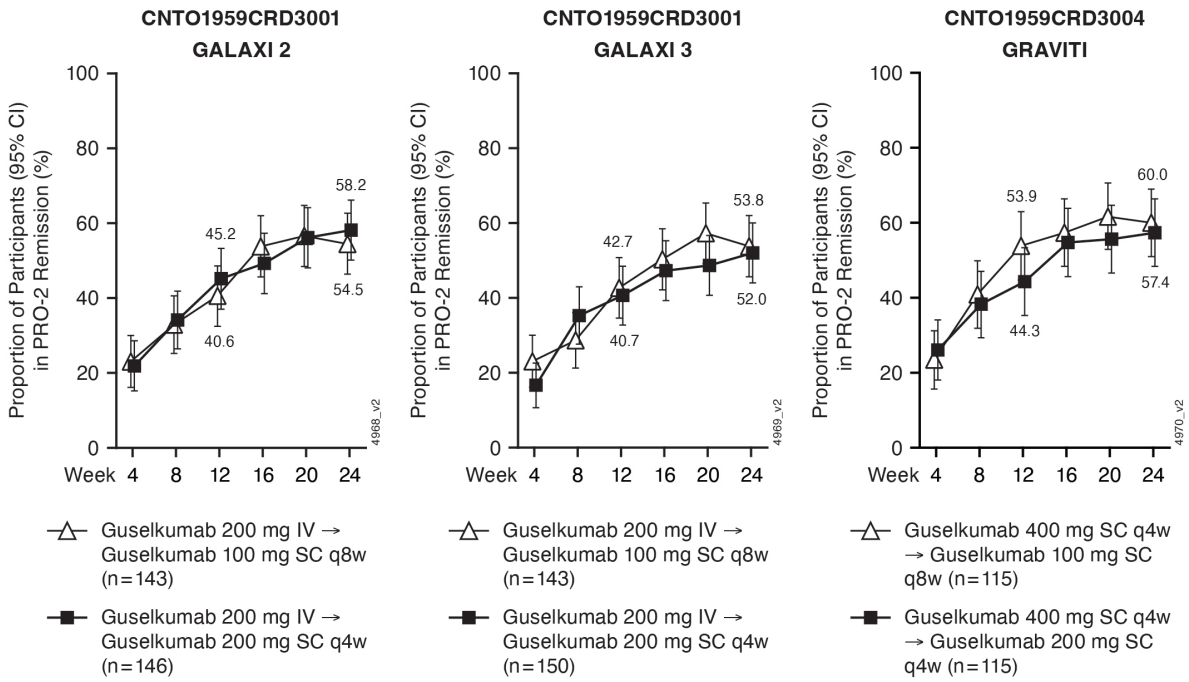
Clinical Endpoints Through Week 24

Figure 41: Clinical Remission Through Week 24; Primary / Full Analysis Set (CNTO1959CRD3001 GALAXI 2, GALAXI 3, and CNTO1959CRD3004 GRAVITI)



Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 42: PRO-2 Remission Through Week 24; Primary / Full Analysis Set (CNTO1959CRD3001 GALAXI 2, GALAXI 3, and CNTO1959CRD3004 GRAVITI)



Note: The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

GALAXI 2, GALAXI 3 and GRAVITI: Subpopulations by BIO-Failure Status

Table 54: Summary of Selected Efficacy Endpoints at Week 12 by Biologic Failure Status and by Study (CNTO1959CRD3001 GALAXI 2, GALAXI 3, and CNTO1959CRD3004 GRAVITI)

	GALAXI 2		GALAXI 3		GRAVITI	
	Placebo	Guselkumab 200 mg IV Combined	Placebo	Guselkumab 200 mg IV Combined	Placebo	Guselkumab 400 mg SC Combined
Analysis set: Primary	76	289	72	293	117	230
Subgroup: BIO-Failure	39	150	39	150	53	108
Clinical remission at Week 12[a,b]	9 (23.1%)	67 (44.7%)	6 (15.4%)	71 (47.3%)	9 (17.0%)	65 (60.2%)
Clinical response at Week 12[a,b]	12 (30.8%)	90 (60.0%)	6 (15.4%)	93 (62.0%)	15 (28.3%)	84 (77.8%)
Endoscopic response at Week 12[a,b]	2 (5.1%)	40 (26.7%)	3 (7.7%)	47 (31.3%)	9 (17.0%)	36 (33.3%)
PRO-2 remission at Week 12[a,b]	5 (12.8%)	61 (40.7%)	5 (12.8%)	59 (39.3%)	9 (17.0%)	56 (51.9%)
Subgroup: CON-Failure	37	139	33	143	64	122
Clinical remission at Week 12[a,b]	8 (21.6%)	69 (49.6%)	5 (15.2%)	67 (46.9%)	16 (25.0%)	64 (52.5%)
Clinical response at Week 12[a,b]	10 (27.0%)	94 (67.6%)	7 (21.2%)	86 (60.1%)	24 (37.5%)	85 (69.7%)
Endoscopic response at Week 12[a,b]	6 (16.2%)	69 (49.6%)	7 (21.2%)	59 (41.3%)	16 (25.0%)	59 (48.4%)
PRO-2 remission at Week 12[a,b]	11 (29.7%)	63 (45.3%)	5 (15.2%)	63 (44.1%)	11 (17.2%)	57 (46.7%)
Subgroup: BIO-Naive	34	121	27	123	56	105
Clinical remission at Week 12[a,b]	6 (17.6%)	60 (49.6%)	4 (14.8%)	61 (49.6%)	14 (25.0%)	52 (49.5%)
Clinical response at Week 12[a,b]	8 (23.5%)	82 (67.8%)	6 (22.2%)	76 (61.8%)	21 (37.5%)	71 (67.6%)
Endoscopic response at Week 12[a,b]	5 (14.7%)	62 (51.2%)	6 (22.2%)	51 (41.5%)	15 (26.8%)	51 (48.6%)
PRO-2 remission at Week 12[a,b]	8 (23.5%)	52 (43.0%)	4 (14.8%)	58 (47.2%)	10 (17.9%)	46 (43.8%)

Clinical remission: CDAI score <150.
Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150.
Endoscopic response: ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2 in GALAXI and ≥50% improvement from baseline in SES-CD score in GRAVITI.
PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.
[a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD or AP or SF score at Week 12 were considered not having achieved the endpoint at Week 12.
Note: CON-Fail includes subjects exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

Pooled analysis of Studies GALAXI 2 and GALAXI 3

Guselkumab Efficacy vs Placebo

Table 55: Summary of the Co-primary and Major Secondary Endpoints – Short-term Placebo-based Comparisons by Biologic Failure Status (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3*)*

	Pooled GALAXI 2 and GALAXI 3	
	Placebo	Guselkumab 200 mg IV Combined
Analysis set: Primary	148	582
Subgroup: BIO-Failure	78	300
Clinical remission at Week 12 [a,b]	15 (19.2%)	138 (46.0%)
Endoscopic response at Week 12 [a,b]	5 (6.4%)	87 (29.0%)
PRO-2 remission at Week 12 [a,b]	10 (12.8%)	120 (40.0%)
Subgroup: CON-Failure	70	282
Clinical remission at Week 12 [a,b]	13 (18.6%)	136 (48.2%)
Endoscopic response at Week 12 [a,b]	13 (18.6%)	128 (45.4%)
PRO-2 remission at Week 12 [a,b]	16 (22.9%)	126 (44.7%)
Subgroup: BIO-Naive	61	244
Clinical remission at Week 12 [a,b]	10 (16.4%)	121 (49.6%)
Endoscopic response at Week 12 [a,b]	11 (18.0%)	113 (46.3%)
PRO-2 remission at Week 12 [a,b]	12 (19.7%)	110 (45.1%)

Clinical remission: CDAI score <150.
Endoscopic response: ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.
PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.
[a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status from that timepoint onwards.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD or AP or SF score at Week 12 were considered not having achieved the endpoint at Week 12.
Note: CON-Fail includes subjects exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

Table 56: Summary of Major Secondary Endpoints – Long-term Placebo-based Comparisons by Biologic Failure Status (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)

	Pooled GALAXI 2 and GALAXI 3		
		Guselkumab	
	Placebo	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w
Analysis set: Primary	148	286	296
Subgroup: BIO-Failure	78	153	147
Corticosteroid-free clinical remission at Week 48[a,b]	10 (12.8%)	65 (42.5%)	73 (49.7%)
Endoscopic response at Week 48[a,b]	5 (6.4%)	52 (34.0%)	47 (32.0%)
Subgroup: CON-Failure	70	133	149
Corticosteroid-free clinical remission at Week 48[a,b]	9 (12.9%)	63 (47.4%)	74 (49.7%)
Endoscopic response at Week 48[a,b]	4 (5.7%)	50 (37.6%)	63 (42.3%)
Subgroup: BIO-Naive	61	116	128
Corticosteroid-free clinical remission at Week 48[a,b]	7 (11.5%)	57 (49.1%)	65 (50.8%)
Endoscopic response at Week 48[a,b]	4 (6.6%)	48 (41.4%)	55 (43.0%)

Corticosteroid-free clinical remission: CDAI score <150 and not receiving corticosteroids at Week 48. Endoscopic response: ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.
[a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], were not in clinical response at Week 12 [ICE6] or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status from that timepoint onwards.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD score at Week 48 were considered not having achieved the endpoint at Week 48.
Note: CON-Fail includes subjects exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

1

Long-term Efficacy: Guselkumab vs Ustekinumab

Table 57: Summary of Region-specific Major Secondary Endpoints – Long-term Ustekinumab-based Comparisons by Biologic Failure Status (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)

	Pooled GALAXI 2 and GALAXI 3		
	Guselkumab		
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Primary	286	296	291
Subgroup: BIO-Failure	153	147	156
Clinical remission at Week 48[a,b]	93 (60.8%)	94 (63.9%)	82 (52.6%)
Endoscopic response at Week 48[a,b]	66 (43.1%)	69 (46.9%)	49 (31.4%)
Endoscopic remission (region-specific) at Week 48[a,b]	32 (20.9%)	21 (14.3%)	21 (13.5%)
PRO-2 remission at Week 48[a,b]	83 (54.2%)	84 (57.1%)	73 (46.8%)
Clinical remission at Week 48 and endoscopic response at Week 48[a,b]	57 (37.3%)	60 (40.8%)	40 (25.6%)
Corticosteroid-free clinical remission at Week 48[a,b]	91 (59.5%)	92 (62.6%)	75 (48.1%)
Subgroup: CON-Failure	133	149	135
Clinical remission at Week 48[a,b]	94 (70.7%)	114 (76.5%)	101 (74.8%)
Endoscopic response at Week 48[a,b]	71 (53.4%)	87 (58.4%)	59 (43.7%)
Endoscopic remission (region-specific) at Week 48[a,b]	40 (30.1%)	42 (28.2%)	27 (20.0%)
PRO-2 remission at Week 48[a,b]	86 (64.7%)	101 (67.8%)	90 (66.7%)
Clinical remission at Week 48 and endoscopic response at Week 48[a,b]	62 (46.6%)	80 (53.7%)	58 (43.0%)
Corticosteroid-free clinical remission at Week 48[a,b]	91 (68.4%)	108 (72.5%)	99 (73.3%)
Subgroup: BIO-Naive	116	128	121
Clinical remission at Week 48[a,b]	85 (73.3%)	98 (76.6%)	91 (75.2%)
Endoscopic response at Week 48[a,b]	68 (58.6%)	76 (59.4%)	52 (43.0%)
Endoscopic remission (region-specific) at Week 48[a,b]	39 (33.6%)	34 (26.6%)	23 (19.0%)

	Pooled GALAXI 2 and GALAXI 3		
	Guselkumab		
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
PRO-2 remission at Week 48[a,b]	76 (65.5%)	86 (67.2%)	81 (66.9%)
Clinical remission at Week 48 and endoscopic response at Week 48[a,b]	59 (50.9%)	70 (54.7%)	52 (43.0%)
Corticosteroid-free clinical remission at Week 48[a,b]	82 (70.7%)	94 (73.4%)	89 (73.6%)

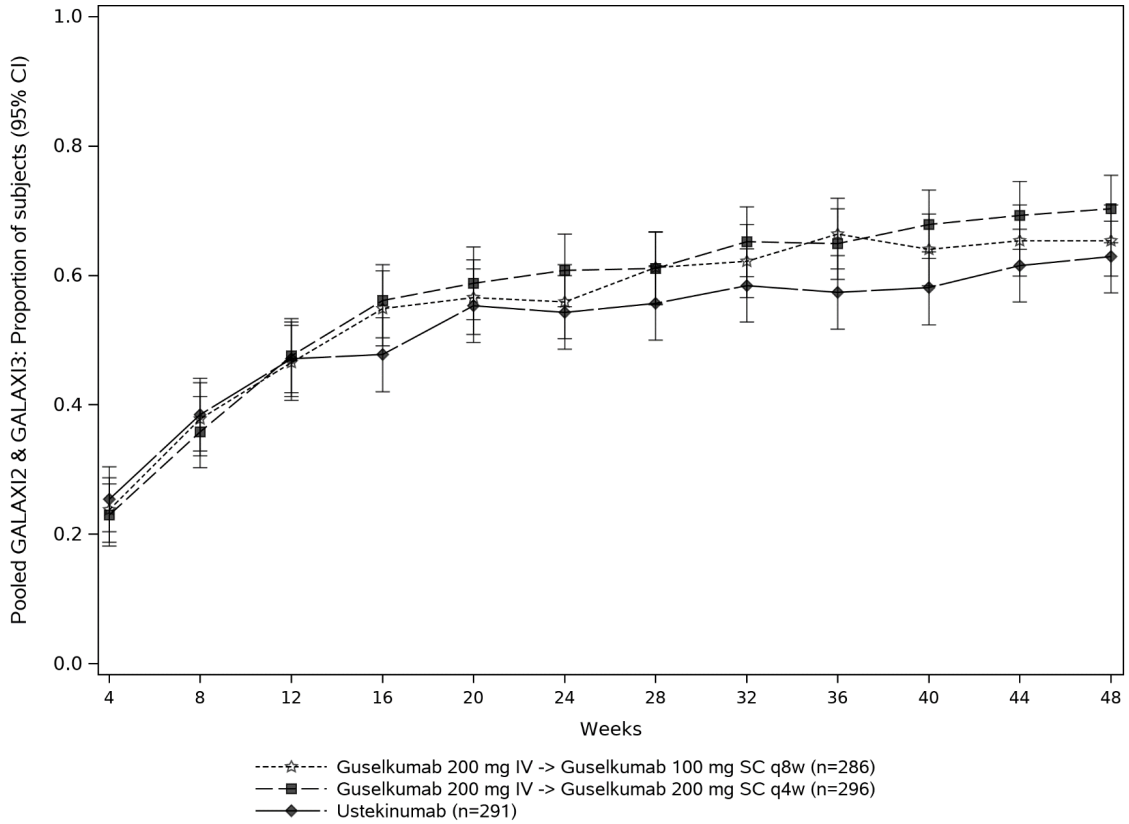
Clinical remission: CDAI score <150. Endoscopic response: ≥ 50% improvement from baseline in SES-CD score or SES-CD Score ≤ 2. Endoscopic remission (region-specific): SES-CD Score ≤ 2. PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline. Corticosteroid-free clinical remission: CDAI score <150 and not receiving corticosteroids at Week 48.

[a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 48.

[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI or SES-CD or AP or SF score at Week 48 were considered not having achieved the endpoint at Week 48.

Note: CON-Fail includes subjects exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

Figure 43: Clinical Remission Through Week 48; Primary Analysis Set (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



Week 48 Clinical Remission Among Week 12 Clinical Non-Responders

Table 58*:* Number of Subjects in Clinical Remission at Week 48 Among Subjects Not Achieving Clinical Response at Week 12; Week 12 Treated Primary Analysis Set (CNTO1959CRD3001 GALAXI 2 and 3)

	Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Week 12 Treated Primary[a]	268	278	546	271
Subset: Subjects not achieving clinical response at Week 12[b,c]	90 (33.6%)	96 (34.5%)	186 (34.1%)	101 (37.3%)
Week 48				
Subjects in clinical remission[b,c,d]	50 (55.6%)	56 (58.3%)	106 (57.0%)	47 (46.5%)
95% CI[e]	(45.3, 65.8)	(48.5, 68.2)	(49.9, 64.1)	(36.8, 56.3)
Adjusted treatment difference (95% CI)[f]	6.6 (-7.7, 20.9)	10.2 (-3.1, 23.5)	8.2 (-3.5, 20.0)	
p-value[g]	0.368	0.134	0.169	

	Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w

Key: ICE=intercurrent event
[a] Week 12 treated primary analysis set includes subjects in the primary analysis set who were treated at Week 12 and did not have ICE 1 - 3 or 5 prior to Week 12.
[b] Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150. Clinical remission is defined as CDAI score <150.
[c] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 non-responder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12 and Week 48.
[d] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48.
[e] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.
[f] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.
[g] The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No).

Upon the CHMP's request, the MAH provided the Week 48 clinical remission rate data for BIO-failed and CON-failed subgroups of Week-12 nonresponder subpopulation:

Table 59: Number of Subjects in Clinical Remission at Week 48 Among Subjects Not Achieving Clinical Response at Week 12; BIO-Failure Subjects in the Week 12 Treated Primary Analysis Set (POOLED CNTO1959CRD3001 GALAXI 2 and 3)

	Pooled GALAXI 2 and GALAXI 3			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Week 12 Treated Primary [a]	268	278	546	271
BIO-Failure Subjects	142	138	280	141
Subset: Subjects not achieving clinical response at Week 12 [b,c]	47 (33.1%)	50 (36.2%)	97 (34.6%)	61 (43.3%)
Week 48 Subjects in clinical remission [b,c,d]	23 (48.9%)	21 (42.0%)	44 (45.4%)	24 (39.3%)
95% CI [e]	(34.6, 63.2)	(28.3, 55.7)	(35.5, 55.3)	(27.1, 51.6)

Key: ICE=intercurrent event
[a] Week 12 treated primary analysis set includes subjects in the primary analysis set who were treated at Week 12 and did not have ICE 1 - 3 or 5 prior to Week 12.
[b] Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150. Clinical remission is defined as CDAI score <150.
[c] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 non-responder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12 and Week 48.
[d] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48.
[e] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.

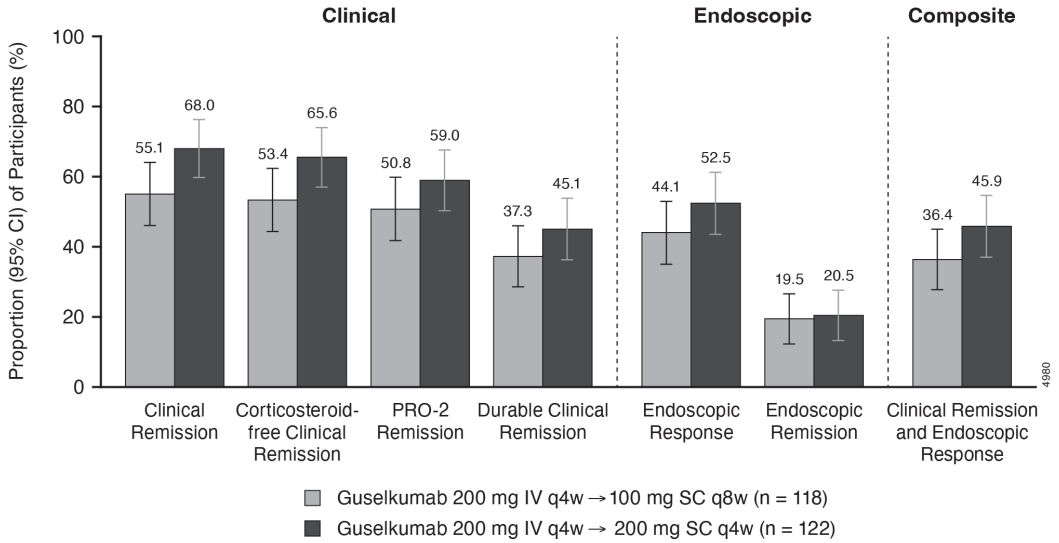
Table 60: Number of Subjects in Clinical Remission at Week 48 Among Subjects Not Achieving Clinical Response at Week 12; CON-Failure Subjects in the Week 12 Treated Primary Analysis Set (POOLED CNTO1959CRD3001 GALAXI 2 and 3)

	Pooled GALAXI 2 and GALAXI 3			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Guselkumab 200 mg IV Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Week 12 Treated Primary [a]	268	278	546	271
CON-Failure Subjects	126	140	266	130
Subset: Subjects not achieving clinical response at Week 12 [b,c]	43 (34.1%)	46 (32.9%)	89 (33.5%)	40 (30.8%)
Week 48				
Subjects in clinical remission [b,c,d]	27 (62.8%)	35 (76.1%)	62 (69.7%)	23 (57.5%)
95% CI [e]	(48.3, 77.2)	(63.8, 88.4)	(60.1, 79.2)	(42.2, 72.8)

Key: ICE=intercurrent event
[a] Week 12 treated primary analysis set includes subjects in the primary analysis set who were treated at Week 12 and did not have ICE 1 - 3 or 5 prior to Week 12.
[b] Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150. Clinical remission is defined as CDAI score <150.
[c] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 non-responder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12 and Week 48.
[d] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48.
[e] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided.
Note: CON-Fail includes subjects exposed to biologic therapy but have not demonstrated inadequate response or intolerance.

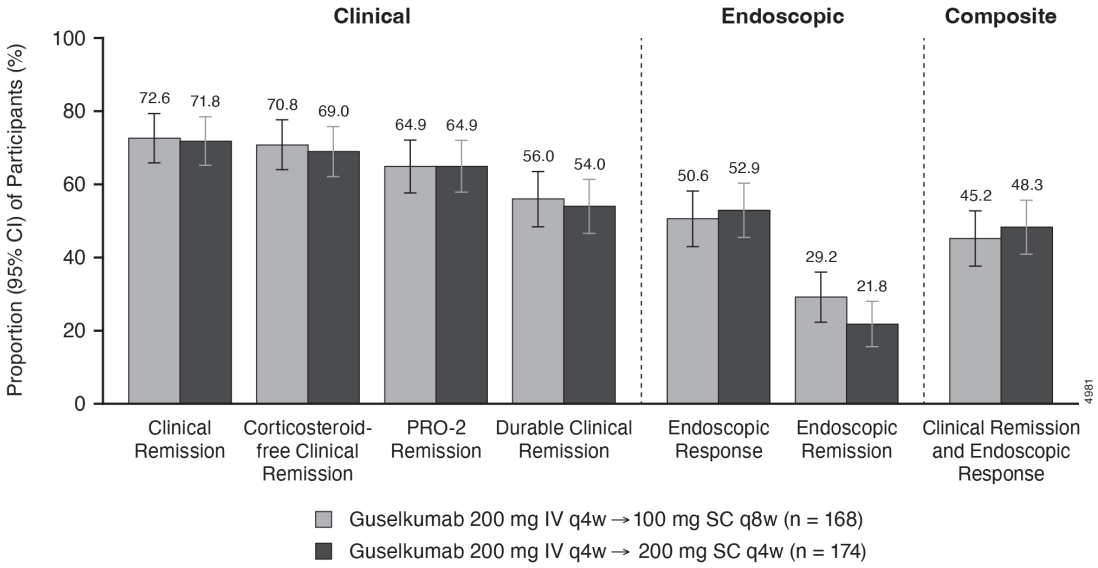
Subgroup Analyses to Evaluate Maintenance Dose Differences (GALAXI 2 and GALAXI 3)

Figure 44: Key Efficacy Endpoints Among Participants with CDAI >300 at Baseline; (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



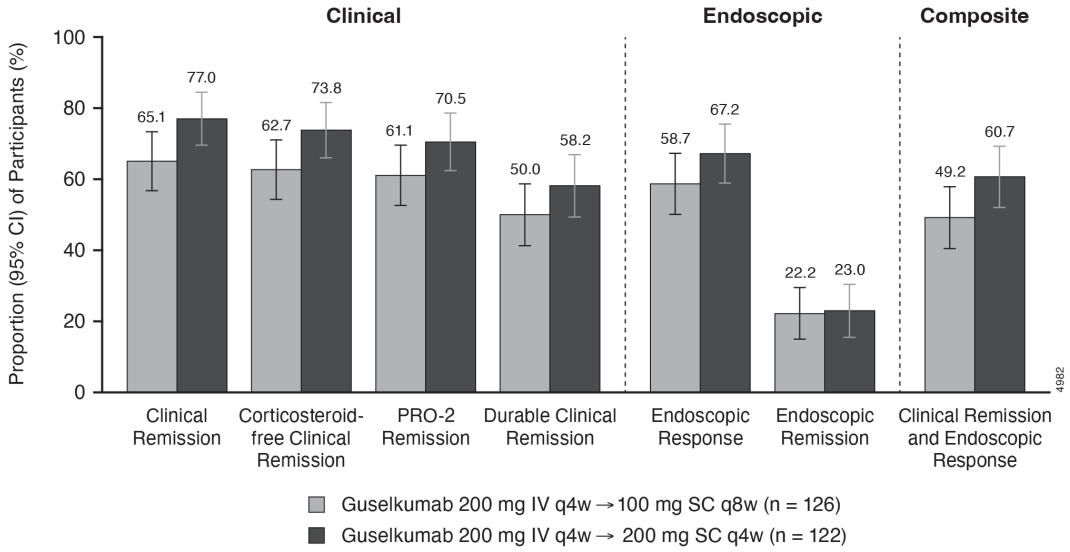
Note: The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 45: Key Efficacy Endpoints Among Participants with CDAI ≤300 at Baseline; (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



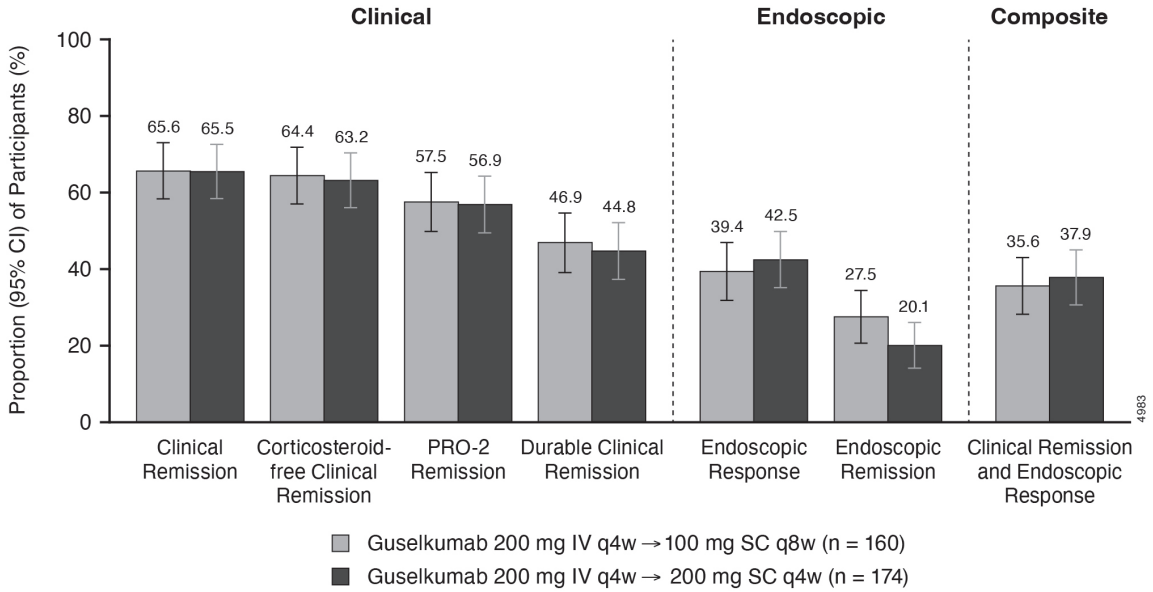
Note: The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 46: Key Efficacy Endpoints Among Participants with SES-CD >12 at Baseline; (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



Note: The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Figure 47: Key Efficacy Endpoints Among Participants with SES-CD ≤12 at Baseline; (POOLED CNTO1959CRD3001 GALAXI 2 and GALAXI 3)



Note: The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

Subgroup Analysis by Disease Severity at Week 12

Greater efficacy of the guselkumab 200 mg SC q4w treatment group compared with the 100 mg SC q8w treatment group was observed for key outcomes at Week 48 according to measures of disease severity at Week 12, including inflammatory burden and response status after induction therapy.

Among participants with an elevated inflammatory burden as evidenced by CRP >5 mg/L at Week 12, guselkumab 200 mg SC q4w achieved a greater proportion in 1) clinical remission at Week 48 (200 mg SC q4w: 71.0% vs 100 mg SC q8w: 54.1%); 2) endoscopic response at Week 48 (200 mg SC q4w: 50.5% vs 100 mg SC q8w: 36.5%); 3) PRO-2 remission at Week 48 (200 mg SC q4w: 61.7% vs 100 mg SC q8w: 51.8%) compared with 100 mg SC q8w in pooled GALAXI 2 and GALAXI 3. This observation was relatively consistent in the individual GALAXI studies with all treatment differences between the 2 guselkumab treatment groups exceeding 5 percentage points for both studies. In contrast, among participants with CRP ≤5 mg/L at Week 12, proportions in the guselkumab 200 mg SC q4w and 100 mg SC q8w treatment groups achieving each of the 3 endpoints above were similar.

Among participants not in endoscopic response at Week 12, a greater proportion of participants achieved endoscopic response at Week 48 with guselkumab 200 mg SC q4w (44.6%) as compared with 100 mg SC q8w (32.1%) in the pooled GALAXI 2 and GALAXI 3 studies. Among participants that were already in endoscopic response at Week 12, similar proportions of participants on guselkumab 200 mg SC q4w and 100 mg SC q8w were able to maintain endoscopic response at Week 48.

Clinical studies in special populations

No clinical studies were conducted in special patient population such as in patients with liver or renal failure.

Of the 1009 Crohn's disease patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, a total of 39 patients were 65 years of age or older, and 5 patients were 75 years of age or older.

2.4.3. Discussion on clinical efficacy

The efficacy of guselkumab for treating moderately to severely active CD was investigated in 4 studies. Three of the studies evaluated guselkumab IV induction followed by SC maintenance (all 3 studies were conducted under a single protocol, CNTO1959CRD3001, hereafter referred to as GALAXI) and the fourth study evaluated guselkumab SC induction followed by SC maintenance (CNTO1959CRD3004; hereafter referred to as GRAVITI).

The GALAXI programme includes 3 separate studies: a 48-week Phase 2 dose-ranging study (GALAXI 1) and two 48-week Phase 3 confirmatory studies (GALAXI 2 and GALAXI 3). All 3 studies were conducted using a treat-through study design. Participants randomized to placebo at Week 0 who did not achieve clinical response at Week 12 crossed over to treatment with the active comparator ustekinumab. Inclusion and exclusion criteria were the same for all GALAXI studies: participants had to be adult patients with active and moderate to severe CD, and with prior failure to conventional or biological therapies (CON-failure and BIO-failure subgroups, respectively).

Dose ranging study GALAXI 1

Methods

In this Phase 2 dose-ranging study, the guselkumab IV dose regimens (200 mg IV, 600 mg IV, and 1200 mg IV) were evaluated to support the induction dose regimens selected for confirmatory evaluation in Phase 3. The 12-week induction phase of the dose-ranging study GALAXI 1 was followed by a maintenance phase through Week 48. Participants who completed the maintenance phase were eligible to enter the LTE to receive approximately 4 additional years of treatment.

The primary efficacy endpoint was the change from baseline of CDAI score at Week 12. CDAI score is considered an appropriate primary efficacy endpoint for the dose-ranging study, since it is expected to be a more sensitive efficacy endpoint compared to a response rate (dichotomous) endpoint. Major secondary endpoints included clinical remission and response rates, as well as PRO-2 remission rate, clinical biomarker response and endoscopic response rate at Week 12. Long-term efficacy endpoints were assessed at Week 48 and were related to clinical symptoms, biomarkers, endoscopic and histologic results and corticosteroid consumption.

A prespecified Week 12 IA was performed during GALAXI 1 to inform Phase 3 induction dosing after the first 250 randomized participants completed Week 12 or terminated study participation before their Week 12 visit. Participants continued to be randomized into the GALAXI 1 study while the prespecified Week 12 IA was ongoing. After the Phase 3 dose selection was made, no further participants were randomized into the GALAXI 1 Phase 2 study.

The GALAXI 1 study was unblinded after the Week 48 DBL and analyses were completed. Results up to Week 152 are available.

Results

Baseline demographic characteristics, baseline CD characteristics and CD-related medication history were generally similar across the treatment groups.

At Week 12 (end of the induction period), the best therapeutic responses were seen for the lowest induction dose (200 mg guselkumab iv. Q4W) for most clinical efficacy endpoints including the primary efficacy endpoint. As for CDAI, numerically better results in all guselkumab treatment groups were seen when compared to ustekinumab. Hence, the 200 mg IV induction dose was selected for evaluation in the Phase 3 studies.

At Week 48, remarkably better outcomes on the majority of key efficacy endpoints were found in the 600 mg iv guselkumab Q4W– 200 mg sc. guselkumab Q4W group compared to the other two guselkumab groups and the ustekinumab induction-ustekinumab maintenance group. The combination of 200 mg iv. guselkumab Q4W induction– 200 mg sc. guselkumab Q4W maintenance was not studied in Study GALAXI 1.

From Week 48 through Week 152, slight decline over time in response/remission rates is observed. This seems to apply for all the three treatment groups. In guselkumab groups, numerically better clinical efficacy results were found at Week 152 compared to ustekinumab group. The decline of remission/response rates was led by the BIO-failed subgroup, while in the CON-failed subgroup the Week 12 clinical outcomes were practically maintained through Week 152. Considering the numerically lower response rate results in the ustekinumab group observed for all subgroups, the decline in the response/remission rates during the long-term extension of GALAXI 1 is not considered to be of concern.

GALAXI 2 and GALAXI 3 studies

Methods

This study enrolled adult participants diagnosed with moderately to severely active CD [baseline CDAI score ≥220 but ≤450 and either mean daily stool frequency count >3 or mean daily AP score >1, SES-CD score ≥6 (or ≥4 for participants with isolated ileal disease)] of at least 3 months duration.

The 4 treatment groups and their corresponding dose regimens from Week 0 through Week 48 were as follows:

- Guselkumab 200 mg IV q4w ×3 induction → 200 mg SC q4w maintenance

- Guselkumab 200 mg IV q4w ×3 induction → 100 mg SC q8w maintenance
- Ustekinumab ~6 mg/kg IV induction → 90 mg SC q8w maintenance as active control
- Placebo iv. → Placebo or Ustekinumab sc Crossover.

According to the treat-through design, participants remained on their assigned treatment regimens for the 48-week study, except for the placebo group, where crossover to sc. ustekinumab treatment was possible when loss of clinical response was detected for the patient in question.

In the GALAXI Phase 3 studies, co-primary endpoints of Clinical remission at Week 12 and Endoscopic response at Week 12 were used. Based on both the 2017 EMA scientific advice recommendation and the endoscopic data from the GALAXI 1 Phase 2 study, the MAH updated the initial primary endpoint of the Phase 3 studies (ie, clinical remission based on CDAI at Week 12) to the co-primary endpoints of Clinical remission at Week 12 (based on CDAI) and Endoscopic response at Week 12. The current version of the EMA Guideline on the development of new medicinal products for the treatment of CD (CPMP/EWP/2284/99 Rev. 2) suggests the co-primary endpoints of symptomatic remission and endoscopic remission, however, this version of the guideline was not yet in force at the time of SA. Therefore, the co-primary endpoints used in the GALAXI 2 and 3 studies are acceptable to the CHMP.

The major secondary endpoints included 3 sets of comparisons. Short-term endpoints at Week 12 (PRO-2 remission, fatigue response and endoscopic remission) evaluated the induction effect of guselkumab compared with placebo.

Long-term endpoints at Week 48 vs placebo (CS-free clinical remission and endoscopic response) evaluated the effect of guselkumab compared with placebo. CS-free remission and PRO based remission were included as Type I error-controlled endpoints, as it was requested in the 2017 EMA SA and follow up SAs.

Long-term endpoints at Week 48 vs ustekinumab (endoscopic remission, clinical remission, endoscopic response, durable clinical remission, PRO-2 remission, CS-free clinical remission and clinical remission plus endoscopic response) evaluated the effect of guselkumab compared with ustekinumab.

Protocol amendments were established for the Phase 3 GALAXI studies to comply with the scientific advices and to adapt from the challenges arising from the COVID-19 pandemic and the Ukrainian war crisis. These amendments are acceptable to the CHMP.

Upon the CHMP's request, the MAH provided further information on the MPD in Studies GALAXI 2 and GALAXI 3. The category of MPD "Other" was led by Clinical laboratory assessments not taken for two or more consecutive visits, and Deviations from approved IPPI process. The MPD category of "Entered but not satisfied criteria" were categorized as CD criteria, laboratory criteria, medication criteria, medical history criteria, and "other". Each MPD was evaluated by the medical monitor and deemed not to impact the participant's efficacy and safety outcomes, and therefore it was considered appropriate for the participant to remain in the study. In Studies GALAXI 2 and GALAXI 3, the average number of MPDs per participant in participants who had MPDs was ≤1.4. The occurrence of MPDs was not connected to a specific site or to a smaller group of sites and was evenly distributed over different countries and sites. Sensitivity analyses for primary and key secondary clinical efficacy endpoints for both Week 12 and Week 48 timepoints showed similar efficacy results with and without exclusion of patients with MPDs. Safety characteristics as well as frequency and event rates of common AEs, serious AE were similar for the safety analysis set with or without patients with MPDs at Week 12 and Week 48. Overall, the CHMP concluded that MPD reported in Studies GALAXI 2 and GALAXI 3 are not expected to affect the study results.

Results

As for participant flow, rates of withdrawal of study treatment were considered high in the active treatment groups of the GALAXI Phase 3 studies. Treatment discontinuation rates were overall higher in the BIO-Failed compared to the CON-Failed subgroup.

The MAH was asked to justify that these treatment withdrawals have not hampered the conclusion of Studies GALAXI 2 and GALAXI 3. In the response, the MAH compared the withdrawal rates with other randomised withdrawal studies in moderate to severe active CD. The withdrawal rates in GALAXI 2 and 3 studies were found to be comparable with the above-mentioned other CD studies. To assess a potential impact of study treatment discontinuation on the conclusions of the GALAXI 2 and GALAXI 3 studies, supportive analyses of the co-primary endpoints (clinical remission at Week 12 and endoscopic response at Week 12) as well as two major secondary endpoints evaluating guselkumab vs placebo (corticosteroid-free clinical remission at Week 48 and endoscopic response at Week 48) were conducted. A different strategy (treatment policy strategy instead of composite strategy) was used to address the intercurrent event of treatment discontinuations not indicative of lack of efficacy. Clinical efficacy outcomes from this sensitivity analysis on the co-primary and two main secondary endpoints showed very similar results. Hence, the issue was not further pursued.

In GALAXI 2 and GALAXI 3 studies, respectively, 52.8% and 51.9% of patients had previously failed treatment with at least one biologic therapy, 41.9% and 41.5% were biologic naïve. At baseline, 37.4% and 36.1% of the patients were receiving oral corticosteroids and 29.9% and 30.2% of the patients were receiving conventional immunomodulators in GALAXI 2 and GALAXI 3 studies, respectively.

The patient population between GALAXI 2 and GALAXI 3 studies are overall comparable in terms of baseline characteristics and CD related characteristics.

Baseline demographics were similar across the treatment groups in the BIO-Failure, CON-Failure, and BIO-Naive subgroups of GALAXI 2 and 3 studies.

According to the EMA SA received in 2017 and also in line with the current EMA Guideline on the development of new medicinal products for the treatment of CD (CPMP/EWP/2284/99 Rev. 2), inclusion criteria for CDAI scores was CDAI scores at screening of 220-450, both inclusively. In Study GALAXI 2, all PAS patients were in this CDAI range. In Study GALAXI 3, 3 patients had a baseline CDAI score <220. Upon the CHMP's request, the MAH clarified that for all 3 concerned patients, incorrect baseline CDAI score was calculated and these errors were picked up in quite a late stage of the maintenance part of GALAXI 3 study. Two of these patients (baseline corrected CDAI scores 209 and 207) were in the ustekinumab group and were compliant to other criteria of moderate-to severe active CD as well as other inclusion and exclusion criteria of the study. For the third patient, a repeated recalculation of the baseline CDAI score resulted in a CDAI score of 224, therefore, no protocol deviation happened in this case.

SES-CD criteria are compliant with the current EMA Guideline on the development of new medicinal products for the treatment of CD (CPMP/EWP/2284/99 Rev. 2) and the 2017 EMA SA.

Concomitant medication was quite balanced between treatment arms in the GALAXI 2 and GALAXI 3 studies except for the overall immunomodulatory drug use, which is slightly higher in the 200 mg iv Q4W – 200 mg maintenance W4Q guselkumab group in GALAXI 3. However, the reported difference is not considered to be relevant.

Clinical efficacy outcomes – GALAXI 2 and GALAXI 3

In study GALAXI 2, co-primary efficacy endpoints and all Tier 1 secondary endpoints (PRO-2 remission vs placebo at Week 12; and CS free clinical remission, endoscopic remission vs placebo at Week 48) were met. In Tier 2 secondary endpoints, only the Week-12 Fatigue response endpoint was met. The

two other Tier 2 endpoints (clinical remission and endoscopic response, endoscopic remission vs ustekinumab at Week 48) failed. However, the clinical efficacy of both guselkumab treatment groups appears numerically better compared to ustekinumab group considering the Week 48 clinical remission and endoscopic remission composite endpoint, and the Week 48 endoscopic remission, CS-free clinical remission and durable clinical remission endpoints.

In study GALAXI 3, co-primary efficacy endpoints and all Tier 1 major secondary endpoints of PRO2 remission vs placebo at Week 12; and CS free remission, endoscopic response vs placebo at Week 48, were met. The Tier 2 key secondary endpoints of fatigue response vs placebo at Week 12, clinical remission and endoscopic response vs ustekinumab at Week 48 were met. The endoscopic remission endpoint at Week 48 vs ustekinumab was met for the 100 mg Q8W guselkumab group, but, failed for the 200 mg Q4W guselkumab group.

At Week 48, similar or higher response rates were observed for the guselkumab 100 mg Q8W sc compared to guselkumab 200 mg sc. Q4W, except for clinical remission and endoscopic response and endoscopic endpoints. Ustekinumab response rates were generally remarkably lower compared to the guselkumab groups.

In GALAXI 2 and GALAXI 3 studies, long term efficacy versus placebo showed significant differences between placebo and guselkumab treatment groups for both maintenance parts in both GALAXI 2 and GALAXI 3 studies. CDAI scores, clinical remission rates and PRO remission rates were in continuous improvement in guselkumab sc. 200 mg Q4W dose group. In the guselkumab sc. 100 mg Q8W dose group, response rates were numerically higher than in the ustekinumab group with the exception of the last, Week 48 observation where there was no numerical difference between the ustekinumab group and the lower guselkumab dose group. Considering the above, the CHMP requested longer term data to present the time course of guselkumab treatment after Week 48. In their response, the MAH clarified that efficacy data after Week 48 are not yet available for GALAXI 2 and GALAXI 3 studies. They further indicated that small fluctuations in the proportions of participants in clinical remission were observed in all GALAXI studies in both maintenance dose groups and was explained by the relapsing-remitting clinical course characteristic of the disease and the relatively variable nature of the CDAI score. Furthermore, the MAH pointed out that persistence of the clinical efficacy through Week 48 in GALAXI 2 and GALAXI 3 studies is supported by the major secondary endpoint of durable clinical remission and sustained clinical remission for both guselkumab SC maintenance dose regimens. The CHMP agreed with the MAH's rationale on the persistence of the clinical efficacy for the 200 mg Q4W and 100 mg Q8W groups. The MAH has committed to submit long-term efficacy results up to 5 years of follow-up of the GALAXI 2 and 3 studies post approval (final report expected in Q3 2028). This is agreed by the CHMP.

The CHMP considered that the posology for the maintenance period initially proposed could be misinterpreted to include a step-up dosing from the 100 mg SC q8w to the 200 mg SC q4w maintenance regimen. However, the MAH clarified that the step-up dosing may be considered only for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgment and Section 4.2 of the SmPC is updated accordingly to avoid misinterpretation.

The effectiveness of step-up dosing from the 100 mg SC q8w to the 200 mg SC q4w maintenance dose regimen is not yet established in CD as it is assessed in the LTE portion of the GALAXI 2 and GALAXI 3 studies for which data are not yet available. The MAH has committed to submit the long-term efficacy results of the GALAXI 2 and GALAXI 3 studies (total duration of follow-up of 5 years) and to discuss the benefits and risks of SC guselkumab maintenance treatment at a dosage of 200 mg q4w in CD patients who have experienced an insufficient response to subcutaneous guselkumab maintenance treatment at a dosage of 100 mg q8w.

Both guselkumab treatment groups showed long-term efficacy at Week 48 endpoints with similar to numerically greater outcomes compared with ustekinumab in BIO-Failure and CON-Failure subpopulations.

In order to address the uncertainty regarding the recommendation to initiate maintenance treatment in BIO-failed patients who are non-responders at Week 12, the MAH provided a pooled efficacy analysis for GALAXI 2 and GALAXI 3 studies for both guselkumab treatment groups who showed clinical remission at Week 48 among participants who did not achieve clinical response at Week 12 in the BIO-Failure and CON-Failure subpopulations. In these analyses, rates of clinical remission in both guselkumab maintenance treatment groups were similar or numerically greater compared with ustekinumab regardless of BIO-Failure status. Both guselkumab maintenance doses are considered efficacious. The response rate was lower in the BIO-failed subgroup, however, this can be expected in a subgroup of patients who failed to respond to a previous biological therapy but also to the guselkumab therapy itself, as well as, since these patients received three iv. induction doses of guselkumab. Nevertheless, clinical remission rate of 45% of guselkumab combined groups in the BIO Failed Week-12 non-responder subgroup is still considered relevant.

Upon the CHMP's request, the MAH agreed to update the posology to consider treatment discontinuation in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment, in line with the protocol of the GALAXI studies.

In GALAXI 2 and GALAXI 3 studies, average daily prednisone dose decreased remarkably from Week 12 and this decrease was maintained through Week 48.

Greater changes from baseline in inflammatory biomarkers (CRP and fecal calprotectin) were observed in the combined guselkumab 200 mg IV treatment group as early as Week 4 and continued to decrease through Week 12 as compared with the placebo treatment group. The change from baseline in the guselkumab treatment groups was generally maintained through Week 48.

Daily average corticosteroid doses decreased remarkably from Week 12, were rather similar for all three treatment groups by Week 48 and seem to be stabilized at around or slightly above 5 mg/day prednisone equivalent dose.

Improvement in PROMIS-Fatigue SF 7a T-scores is observed at week 12 and week 48 in GALAXI 2 and GALAXI 3 studies. Upon the CHMP's request, the MAH clarified that ≥7 point improvement from baseline was used for all 3 PROMIS measures (PROMIS-Fatigue SF-7a, PROMIS-29 PCS and PROMIS-29 MCS) to define the within-patient minimal clinically important change. The MAH acknowledged that the LS mean differences between groups in PROMIS-Fatigue SF-7a T-score (3.7), PROMIS-29 MCS (2.6) and PCS T-scores (3.4) did not achieve the threshold. However, the within-patient comparison threshold cannot be applied to between-group meaningful comparisons. The CHMP noted also that the MAH received SA from the CHMP (EMA/SA/0000129794) on the development of PROMIS-29 and PROMIS-Fatigue Short Form 7a PROs to evaluate treatment benefit in patients with CD or ulcerative colitis. However, as recommended during the SA given while the concerned phase-3 studies were ongoing, any communication strategy for PROMIS-29 and implementation in the analysis plan would have required preceding agreement on how to score and convey the results. The inclusion of fatigue responses in SmPC Section 5.1 is agreed by the CHMP as it is supported by type-I error controlled Week-12 Fatigue response rate results and the maintenance of Fatigue response by Week-48 in GALAXI 2 and GALAXI 3 studies, which is considered clinically relevant.

The MAH argumented to include IBDQ and PROMIS-29 in SmPC Section 5.1. The MAH's rationale to include PROMIS-29 was based on the similarity to the SF-36 that are generally not multiplicity controlled outcomes but still included in the SmPC of other biologicals approved in the treatment of CD. The CHMP noted that for PROMIS-29 outcomes of sleep disturbance and ability to participate in

social roles and activity domains, ustekinumab became better than gusekumab by Week 48. Considering the lack of Type 1 error control for PROMIS-29 and the not so remarkable effect sizes for for PROMIS-29 measures, the CHMP did not agree with the inclusion of PROMIS-29 in the SmPC Section 5.1.

Based upon the MAH's response, the CHMP considered the results on IBDQ total domain score clinically relevant, hence, agreed to include them in the SmPC Section 5.1.

GRAVITI study

GRAVITI is an ongoing, Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in patients with moderately to severely active CD who had an inadequate response to or intolerance of prior conventional therapy (ie, oral corticosteroids or immunomodulators [6-MP/AZA/MTX]) or biologic therapy (ie, TNF antagonists or vedolizumab).

Similar to GALAXI, the GRAVITI study was conducted using a treat-through study design though the rescue criteria and rescue agent (guselkumab) were different. GRAVITI consists of a 24-week main study part with a long-term extension through Week 248. The overall GRAVITI study duration is up to 265 weeks.

GRAVITI study has the same co-primary endpoints (clinical remission at Week 12 and endoscopic response at week 12) as GALAXI 2 and GALAXI 3 studies.

Results

The co-primary endpoints (clinical remission at Week 12 and endoscopic response at Week 12) were met for the guselkumab (400 mg SC) treatment group. Additionally, all secondary endpoints (clinical remission at Week 24 [for both guselkumab treatment groups], PRO-2 remission at Week 12, and clinical response at Week 12) were achieved.

The efficacy on clinical remission and endoscopic response was maintained at Week 48.

The proportions of participants who were in CS-free clinical remission at Week 48 were greater in the guselkumab treatment groups compared with the placebo treatment group. Most of the participants in both guselkumab treatment groups who achieved clinical remission at Week 48, were corticosteroid-free. Among participants receiving corticosteroids at baseline, higher proportions of participants in the guselkumab treatment groups had completed corticosteroid tapering and were in corticosteroid-free clinical remission at Week 48 compared to the placebo group.

Treatment with guselkumab resulted in reduction in markers of inflammation in the guselkumab treatment groups compared with the placebo group over time, starting at Week 4.

Consistent with clinical endpoints, improvements over time were observed in patient-reported GI symptoms and in HRQOL among participants who received guselkumab.

Comparison between GALAXI studies and GRAVITI study

Across all 3 studies, median CD duration, median CDAI score, median SES-CD score, and disease location were similar and consistent with a population of participants with moderately to severely active CD.

Ratio of patients with ileum and colon involvement was slightly higher in the GRAVITI study. However, other disease related parameters do not show higher disease burden for the patient population in the GRAVITI study. Proportion of BIO-failed subjects is also lower in GRAVITI study. Participants in these studies had clinically active disease defined as baseline CDAI score ≥220 but ≤450. However, there was

a difference in the inclusion criteria of mean daily stool frequency and abdominal pain counts: participants were required to have either a mean daily stool frequency count >3 in GALAXI studies and ≥4 in GRAVITI study, based on the unweighted CDAI component of the number of liquid or very soft stools or a mean daily abdominal pain score >1 in GALAXI studies and ≥2 in GRAVITI study, based on the unweighted CDAI component of abdominal pain. However, the median baseline abdominal pain and stool frequency were similar across all studies, such that the difference in the inclusion criteria did not have a substantial impact on the symptomatic severity of the population enrolled in the GALAXI and GRAVITI studies. Overall, the CHMP concluded that the population are sufficiently comparable.

Use of concomitant medication in general and use of CSs was slightly lower in the GRAVITI study. However, the difference is not expected to hamper the comparability between the studies.

Albeit the clinical remission and response rates that were higher in the combined guselkumab group of GRAVITI study at Week 12 compared to the combined guselkumab groups of GALAXI 2 and 3 studies, the effect sizes are overall similar, due to the higher placebo response in the GRAVITI study.

At the later Week 24 timepoint, the clinical remission rate was slightly higher in the 200 mg sc. Q4W guselkumab group of study GALAXI 2 compared to the 100 mg sc. Q8W group. There was no difference between the two guselkumab regimens by Week 24 in GALAXI 3 and GRAVITI studies. Slightly higher clinical remission rates were observed in the 100 mg sc. Q8W treatment group in GRAVITI study.

Comparison of the results from the GRAVITI study to the GALAXI 2 and 3 studies up to Week 24 indicate that the guselkumab 400 mg SC induction dose achieves comparable outcomes to the IV 200 mg induction dose in participants with moderately to severely active CD. The comparable efficacy of the 400 mg SC induction dose and the 200 mg IV induction dose was further confirmed by the comparable results of clinical remission at Week 24 and similarity in response curves over time through Week 24.

The MAH applied to include an indication *for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.* The CHMP noted that, as for prior medication, BIO-failed patient populations of GALAXI and GRAVITI studies failed only TNF-alpha inhibitor and/or vedolizumab therapy(ies). In line with the approach taken for other medicinal products for the same or similar indications, the indication, as proposed by the MAH, was acceptable to the CHMP. The information in respect to previous treatment failure (i.e.the proportion of patients with prior TNFa failure/intolerance and vedolizumab failure/intolerance) has been added to section 5.1 of the SmPC**.**

2.4.4. Conclusions on the clinical efficacy

Guselkumab induction and maintenance treatment was effective in moderately to severely active CD patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.

Both induction doses of 200 mg iv. and 400 mg sc. at Week 0, 4 and 8 are effective. The recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgment, a maintenance dose regimen of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered. Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.

2.5. Clinical safety

Introduction

Guselkumab, an IL-23p19 antagonist, has a well-characterized safety profile established both in clinical studies across multiple indications and in approximately 6 years of postmarketing experience in the approved psoriatic indications. The estimated cumulative global exposure to guselkumab from launch through 30 June 2023 is 407,104 person-years.

Several biologics in the IL-23 inhibitor class have been approved across a number of indications, establishing a stable and well-characterized safety profile for the mechanism of action. Common warnings and precautions and related adverse drug reactions shared across molecules include infections (eg, upper respiratory tract infections, gastroenteritis), hypersensitivity reactions (eg, infusion and injection site reactions), and liver enzyme elevations.

The key safety data to evaluate the safety of guselkumab therapy in patients with moderately to severely active CD are from GALAXI studies, including 12 weeks IV induction followed by SC maintenance through Week 48, and GRAVITI study, including 12 weeks SC induction followed by SC maintenance through Week 24. During the procedure, the MAH provided safety data up to Week 48 for the GRAVITI study.

Supportive safety data are provided from the UC studies (ie, CNTO1959UCO3001, hereafter referred to as QUASAR Phase 2b induction study [IS-1], QUASAR Phase 3 induction study [IS-2], QUASAR Phase 3 Maintenance Study, and CNTO1959UCO2002, hereafter referred to as VEGA Phase 2a study), and Phase 2 and 3 studies in the approved indications of plaque psoriasis and PsA.

Patient exposure

Placebo-controlled Induction

A summary of guselkumab exposure through reporting period up to approximately one year is provided in Table 61.

Table 61: Summary of Guselkumab Exposure Through Reporting Period up to Approximately One Year; CD Safety, Phase 2/3 Studies Analysis Set

	GALAXI 1, 2, 3 (0-48 weeks)[a]					GRAVITI (0-24 weeks)[a]			CD Combined [a]
	Guselkumab					Guselkumab			
	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	600 mg IV q4w → 200 mg SC q4w	1200 mg IV q4w → 200 mg SC q4w	All GUS	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	All GUS[b]	All GUS[b]
Analysis set: CD Safety, Phase 2/3 Studies	353	296	65	65	780	115	115	274	1054
Duration of guselkumab exposure[c]									
At least 6 months[d]	326 (92.4%)	283 (95.6%)	53 (81.5%)	50 (76.9%)	712 (91.3%)	113 (98.3%)	114 (99.1%)	227 (82.8%)	939 (89.1%)
At least 1 year[e]	296 (83.9%)	268 (90.5%)	52 (80.0%)	45 (69.2%)	661 (84.7%)	0	0	0	661 (62.7%)
Average duration of guselkumab treatment (weeks)[c]	36.3	41.6	36.2	32.8	37.9	16.3	20.1	15.9	32.2
Total dose (mg)									
N	353	296	65	65	780	115	115	274	1054
Mean (SD)	943.1 (199.75)	2258.4 (455.02)	3070.8 (1051.45)	4483.1 (1534.15)	1913.5 (1232.68)	1298.3 (13.13)	1786.1 (131.71)	1421.5 (366.56)	1785.6 (1097.97)
Median	1000.0	2400.0	3600.0	5400.0	1400.0	1300.0	1800.0	1300.0	1300.0
Range	(200; 2000)	(200; 3400)	(600; 3600)	(1200; 5400)	(100; 5400)	(1200; 1300)	(400; 1800)	(400; 1800)	(100; 5400)
IQ range	(1000.0; 1000.0)	(2400.0; 2400.0)	(3600.0; 3600.0)	(4200.0; 5400.0)	(1000.0; 2400.0)	(1300.0; 1300.0)	(1800.0; 1800.0)	(1300.0; 1800.0)	(1000.0; 2400.0)

[a] Crohn's disease: (0-48 weeks) CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3; (0-24 weeks) CNTO1959CRD3004 GRAVITI.
[b] Data after a subject is rescued with guselkumab are included in the All GUS column.
[c] Cumulative guselkumab treatment duration was computed from the first dose to the last dose of guselkumab.
[d] The duration between the first and last guselkumab administration was at least 12 weeks.
[e] The duration between the first and last guselkumab administration was at least 36 weeks.
Note: Includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].

Exposure in IBD

In the IBD Safety Phase 3 Analysis Set, 1233 participants were exposed to guselkumab during the placebo-controlled induction period. Among these participants, 1003 received guselkumab 200 mg IV and 230 received guselkumab 400 mg SC (Table 62).

Table 62: Summary of Guselkumab Exposure During Placebo-controlled Induction Period (Week 0 to Week 12); IBD Safety, Phase 3 Studies Analysis Set

		Crohn's Disease[a]			Inflammatory Bowel Disease[a]	
	Ulcerative Colitis[a]	GALAXI 2, 3	GRAVITI	CD Combined	Guselkumab	
	GUS 200 mg IV q4w	GUS 200 mg IV q4w	GUS 400 mg SC q4w	All GUS	COMB 200 mg IV q4w	All GUS
Analysis set: IBD Safety, Phase 3 Studies	421	582	230	812	1003	1233
Total number of administrations (IV or SC)						
1	12 (2.9%)	5 (0.9%)	1 (0.4%)	6 (0.7%)	17 (1.7%)	18 (1.5%)
2	9 (2.1%)	8 (1.4%)	0	8 (1.0%)	17 (1.7%)	17 (1.4%)
3	400 (95.0%)	569 (97.8%)	229 (99.6%)	798 (98.3%)	969 (96.6%)	1198 (97.2%)
Average duration of guselkumab treatment (weeks)	7.9	8.1	8.2	8.2	8.0	8.1
Total dose (mg)						
N	421	582	230	812	1003	1233
Mean (SD)	585.3 (73.04)	602.9 (103.01)	1196.5 (52.75)	771.1 (282.87)	595.5 (92.00)	707.6 (249.50)
Median	600.0	600.0	1200.0	600.0	600.0	600.0
Range	(200; 800)	(200; 1600)	(400; 1200)	(200; 1600)	(200; 1600)	(200; 1600)
IQ range	(600.0; 600.0)	(600.0; 600.0)	(1200.0; 1200.0)	(600.0; 1200.0)	(600.0; 600.0)	(600.0; 600.0)

Adverse events

A summary of Treatment-emergent Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12) is provided in Table 63.

Table 63: Overall Summary of Treatment-emergent Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12); CD Safety, Phase 2/3 Studies Analysis Set

	GALAXI 1, 2, 3[a]						GRAVITI[a]		CD Combined[a]	
		Guselkumab								
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w	All GUS[b]	UST	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]
Analysis set: CD Safety, Phase 2/3 Studies	211	649	65	65	779	359	117	230	328	1009
Average duration of follow-up (weeks)	12.2	12.3	11.9	11.7	12.3	12.3	12.0	12.3	12.1	12.3
Average exposure (number of administrations)	2.9	2.9	2.7	2.7	2.9	2.0	2.9	3.0	2.9	2.9
Subjects who died	0	0	0	0	0	0	0	1 (0.4%)	0	1 (0.1%)
Subjects with 1 or more:										
Adverse events	109 (51.7%)	304 (46.8%)	33 (50.8%)	29 (44.6%)	366 (47.0%)	168 (46.8%)	58 (49.6%)	106 (46.1%)	167 (50.9%)	472 (46.8%)
Adverse events by maximum intensity[c]										
Mild	55 (26.1%)	181 (27.9%)	15 (23.1%)	16 (24.6%)	212 (27.2%)	89 (24.8%)	24 (20.5%)	65 (28.3%)	79 (24.1%)	277 (27.5%)
Moderate	46 (21.8%)	102 (15.7%)	17 (26.2%)	12 (18.5%)	131 (16.8%)	66 (18.4%)	29 (24.8%)	38 (16.5%)	75 (22.9%)	169 (16.7%)
Severe	8 (3.8%)	21 (3.2%)	1 (1.5%)	1 (1.5%)	23 (3.0%)	13 (3.6%)	5 (4.3%)	3 (1.3%)	13 (4.0%)	26 (2.6%)
Serious adverse events	13 (6.2%)	19 (2.9%)	3 (4.6%)	1 (1.5%)	23 (3.0%)	20 (5.6%)	9 (7.7%)	5 (2.2%)	22 (6.7%)	28 (2.8%)
Adverse events leading to discontinuation of study agent	9 (4.3%)	11 (1.7%)	0	1 (1.5%)	12 (1.5%)	8 (2.2%)	3 (2.6%)	1 (0.4%)	12 (3.7%)	13 (1.3%)
Infections[d]	38 (18.0%)	110 (16.9%)	11 (16.9%)	11 (16.9%)	132 (16.9%)	61 (17.0%)	24 (20.5%)	43 (18.7%)	62 (18.9%)	175 (17.3%)
Serious infections[d]	0	1 (0.2%)	1 (1.5%)	0	2 (0.3%)	6 (1.7%)	0	1 (0.4%)	0	3 (0.3%)

[a] CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3; CNTO1959CRD3004 GRAVITI.
[b] Subjects not randomized to guselkumab who inadvertently received at least one dose of guselkumab are included in the All GUS column for GALAXI studies. Subjects randomized to guselkumab who received an incorrect treatment of ustekinumab are included in their randomized treatment columns.
[c] The maximum severity event experienced by the subject is used.
[d] Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'.
Note: Includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].

Common AEs

Table 64: Number of subjects with one or more treatment-emergent adverse events with frequency of 5% or greater in any treatment group through week 12 by MedDRA preferred term; Safety analysis set (GALAXI 1)

		Guselkumab				
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w	Combined	Ustekinumab[a]
Analysis set: Safety analysis set	70	73	73	73	219	71
Average duration of follow-up (weeks)	12.1	12.2	12.0	11.7	12.0	12.2
Average exposure (number of study agent administrations)	2.8	2.7	2.7	2.7	2.7	1.9
Subjects with 1 or more adverse events	42 (60.0%)	32 (43.8%)	37 (50.7%)	31 (42.5%)	100 (45.7%)	36 (50.7%)
Preferred term						
Headache	0	2 (2.7%)	5 (6.8%)	5 (6.8%)	12 (5.5%)	1 (1.4%)
Nasopharyngitis	3 (4.3%)	3 (4.1%)	4 (5.5%)	3 (4.1%)	10 (4.6%)	3 (4.2%)
Anaemia	5 (7.1%)	1 (1.4%)	3 (4.1%)	2 (2.7%)	6 (2.7%)	2 (2.8%)
Arthralgia	2 (2.9%)	2 (2.7%)	3 (4.1%)	1 (1.4%)	6 (2.7%)	4 (5.6%)
Haemoglobin decreased	5 (7.1%)	1 (1.4%)	1 (1.4%)	2 (2.7%)	4 (1.8%)	0
Upper respiratory tract infection	4 (5.7%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (1.4%)	4 (5.6%)
Abdominal pain	3 (4.3%)	1 (1.4%)	0	1 (1.4%)	2 (0.9%)	4 (5.6%)

IV=intravenous; q4w=every 4 weeks; SC=subcutaneous.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.
a: Subjects received a single ustekinumab IV induction dose at Week 0. At Week 8, subjects received one ustekinumab SC maintenance (90 mg SC) dose.

Table 65: Number of subjects with treatment-emergent adverse events with frequency of at least 3% in any treatment group through week 48 by preferred term; Primary safety analysis set (GALAXI 2)

	Placebo			Guselkumab			
	Placebo[a]	Placebo → Ustekinumab[b]	Combined (As Randomized)[c]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Primary safety	76	49	76	143	146	289	143
Average duration of follow-up (weeks)	22.3	35.3	45.0	47.1	47.8	47.4	45.8
Average exposure (number of administrations)	5.2	4.8	8.3	6.7	11.7	9.2	5.6
Subjects with 1 or more adverse events	38 (50.0%)	27 (55.1%)	53 (69.7%)	106 (74.1%)	115 (78.8%)	221 (76.5%)	112 (78.3%)
Preferred term							
COVID-19	2 (2.6%)	7 (14.3%)	9 (11.8%)	18 (12.6%)	22 (15.1%)	40 (13.8%)	22 (15.4%)
Arthralgia	3 (3.9%)	3 (6.1%)	6 (7.9%)	13 (9.1%)	14 (9.6%)	27 (9.3%)	12 (8.4%)
Upper respiratory tract infection	3 (3.9%)	2 (4.1%)	4 (5.3%)	14 (9.8%)	12 (8.2%)	26 (9.0%)	9 (6.3%)
Crohn's disease	9 (11.8%)	3 (6.1%)	12 (15.8%)	13 (9.1%)	12 (8.2%)	25 (8.7%)	14 (9.8%)
Abdominal pain	3 (3.9%)	1 (2.0%)	4 (5.3%)	11 (7.7%)	9 (6.2%)	20 (6.9%)	12 (8.4%)
Headache	2 (2.6%)	1 (2.0%)	3 (3.9%)	4 (2.8%)	16 (11.0%)	20 (6.9%)	13 (9.1%)
Anaemia	3 (3.9%)	1 (2.0%)	3 (3.9%)	8 (5.6%)	10 (6.8%)	18 (6.2%)	10 (7.0%)
Nasopharyngitis	2 (2.6%)	1 (2.0%)	3 (3.9%)	7 (4.9%)	10 (6.8%)	17 (5.9%)	12 (8.4%)
Pyrexia	4 (5.3%)	1 (2.0%)	5 (6.6%)	9 (6.3%)	8 (5.5%)	17 (5.9%)	14 (9.8%)
Back pain	2 (2.6%)	0	2 (2.6%)	5 (3.5%)	6 (4.1%)	11 (3.8%)	3 (2.1%)
Diarrhoea	0	1 (2.0%)	1 (1.3%)	5 (3.5%)	5 (3.4%)	10 (3.5%)	2 (1.4%)
Nausea	1 (1.3%)	0	1 (1.3%)	4 (2.8%)	5 (3.4%)	9 (3.1%)	6 (4.2%)
Constipation	0	0	0	5 (3.5%)	3 (2.1%)	8 (2.8%)	3 (2.1%)
Abdominal pain upper	2 (2.6%)	0	2 (2.6%)	3 (2.1%)	3 (2.1%)	6 (2.1%)	5 (3.5%)
Lymphocyte count decreased	0	1 (2.0%)	1 (1.3%)	5 (3.5%)	1 (0.7%)	6 (2.1%)	0
Influenza	2 (2.6%)	1 (2.0%)	3 (3.9%)	3 (2.1%)	2 (1.4%)	5 (1.7%)	1 (0.7%)
Vomiting	2 (2.6%)	0	2 (2.6%)	2 (1.4%)	3 (2.1%)	5 (1.7%)	7 (4.9%)
Sinusitis	1 (1.3%)	2 (4.1%)	3 (3.9%)	1 (0.7%)	2 (1.4%)	3 (1.0%)	1 (0.7%)
Alopecia	0	0	0	2 (1.4%)	0	2 (0.7%)	5 (3.5%)
Insomnia	2 (2.6%)	1 (2.0%)	3 (3.9%)	1 (0.7%)	0	1 (0.3%)	2 (1.4%)
Thrombocytosis	1 (1.3%)	2 (4.1%)	2 (2.6%)	0	0	0	1 (0.7%)
Weight decreased	2 (2.6%)	1 (2.0%)	3 (3.9%)	0	0	0	0

Table 66: Number of subjects with treatment-emergent adverse events with frequency of at least 3% in any treatment group through week 48 by preferred term; Primary safety analysis set (GALAXI 3)

	Placebo			Guselkumab			
	Placebo[a]	Placebo → Ustekinumab[b]	Combined (As Randomized)[c]	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Combined	Ustekinumab ~6 mg/kg IV → 90 mg SC q8w
Analysis set: Primary safety	72	49	72	143	150	293	148
Average duration of follow-up (weeks)	20.5	34.0	43.5	45.3	45.5	45.4	44.9
Average exposure (number of administrations)	4.8	4.6	7.9	6.4	10.9	8.7	5.4
Subjects with 1 or more adverse events	41 (56.9%)	33 (67.3%)	56 (77.8%)	113 (79.0%)	115 (76.7%)	228 (77.8%)	117 (79.1%)
Preferred term							
COVID-19	7 (9.7%)	5 (10.2%)	12 (16.7%)	25 (17.5%)	31 (20.7%)	56 (19.1%)	15 (10.1%)
Upper respiratory tract infection	3 (4.2%)	4 (8.2%)	7 (9.7%)	14 (9.8%)	13 (8.7%)	27 (9.2%)	13 (8.8%)
Crohn's disease	11 (15.3%)	6 (12.2%)	16 (22.2%)	12 (8.4%)	14 (9.3%)	26 (8.9%)	11 (7.4%)
Arthralgia	1 (1.4%)	2 (4.1%)	3 (4.2%)	9 (6.3%)	11 (7.3%)	20 (6.8%)	8 (5.4%)
Headache	4 (5.6%)	0	4 (5.6%)	9 (6.3%)	8 (5.3%)	17 (5.8%)	6 (4.1%)
Pyrexia	3 (4.2%)	3 (6.1%)	6 (8.3%)	9 (6.3%)	8 (5.3%)	17 (5.8%)	12 (8.1%)
Nasopharyngitis	2 (2.8%)	1 (2.0%)	3 (4.2%)	4 (2.8%)	11 (7.3%)	15 (5.1%)	7 (4.7%)
Abdominal pain	5 (6.9%)	0	5 (6.9%)	8 (5.6%)	5 (3.3%)	13 (4.4%)	14 (9.5%)
Anaemia	4 (5.6%)	3 (6.1%)	6 (8.3%)	7 (4.9%)	5 (3.3%)	12 (4.1%)	6 (4.1%)
Influenza	0	0	0	7 (4.9%)	3 (2.0%)	10 (3.4%)	3 (2.0%)
Injection site erythema	0	0	0	6 (4.2%)	3 (2.0%)	9 (3.1%)	1 (0.7%)
Pruritus	0	0	0	3 (2.1%)	6 (4.0%)	9 (3.1%)	4 (2.7%)
Nausea	6 (8.3%)	0	6 (8.3%)	4 (2.8%)	4 (2.7%)	8 (2.7%)	4 (2.7%)
Rash	2 (2.8%)	0	2 (2.8%)	3 (2.1%)	5 (3.3%)	8 (2.7%)	0
Hypertension	1 (1.4%)	0	1 (1.4%)	5 (3.5%)	2 (1.3%)	7 (2.4%)	2 (1.4%)
White blood cell count decreased	1 (1.4%)	0	1 (1.4%)	2 (1.4%)	5 (3.3%)	7 (2.4%)	1 (0.7%)
Alanine aminotransferase increased	1 (1.4%)	0	1 (1.4%)	1 (0.7%)	5 (3.3%)	6 (2.0%)	0
Diarrhoea	2 (2.8%)	1 (2.0%)	3 (4.2%)	3 (2.1%)	3 (2.0%)	6 (2.0%)	11 (7.4%)
Respiratory tract infection	1 (1.4%)	1 (2.0%)	2 (2.8%)	0	6 (4.0%)	6 (2.0%)	3 (2.0%)
Eczema	0	2 (4.1%)	2 (2.8%)	1 (0.7%)	3 (2.0%)	4 (1.4%)	0
Urinary tract infection	0	1 (2.0%)	1 (1.4%)	1 (0.7%)	3 (2.0%)	4 (1.4%)	6 (4.1%)
Fatigue	0	0	0	3 (2.1%)	0	3 (1.0%)	6 (4.1%)
Anal fistula	4 (5.6%)	2 (4.1%)	5 (6.9%)	1 (0.7%)	1 (0.7%)	2 (0.7%)	3 (2.0%)
Haemorrhoids	2 (2.8%)	0	2 (2.8%)	1 (0.7%)	1 (0.7%)	2 (0.7%)	5 (3.4%)
Sinusitis	1 (1.4%)	2 (4.1%)	3 (4.2%)	2 (1.4%)	0	2 (0.7%)	4 (2.7%)
Flatulence	0	1 (2.0%)	1 (1.4%)	0	0	0	5 (3.4%)

[a] Events in this column are attributed to those subjects randomized to placebo with one exception: in the case where a subject is randomized to placebo and crosses over to ustekinumab, events occurring after receiving ustekinumab are not counted in this column.
[b] Subjects who are placebo nonresponders and crossed over to ustekinumab at Week 12. Events counted in this group occurred after the subject switched to the ustekinumab treatment group.
[c] This includes all events in the randomized placebo group regardless of crossover to ustekinumab at or after week 12.
Note: Subjects are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.0.

Table 67: Number of subjects with treatment-emergent adverse events with frequency of at least 3% in any treatment group through week 48 by preferred term; Primary safety analysis set (GRAVITI)

			Guselkumab			
	Placebo[a]	Placebo → Guselkumab[b]	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	Combined	All Guselkumab
Analysis set: Safety	117	44	115	115	230	274
Average duration of follow-up (weeks)	30.0	30.6	47.0	48.0	47.5	44.8
Average exposure (number of study agent administrations)	7.1	4.7	6.8	11.8	9.3	8.5
Subjects with 1 or more adverse events	77 (65.8%)	33 (75.0%)	95 (82.6%)	92 (80.0%)	187 (81.3%)	220 (80.3%)
Preferred term						
Upper respiratory tract infection	12 (10.3%)	8 (18.2%)	15 (13.0%)	15 (13.0%)	30 (13.0%)	38 (13.9%)
Abdominal pain	7 (6.0%)	3 (6.8%)	10 (8.7%)	14 (12.2%)	24 (10.4%)	27 (9.9%)
COVID-19	8 (6.8%)	1 (2.3%)	11 (9.6%)	11 (9.6%)	22 (9.6%)	23 (8.4%)
Crohn's disease	23 (19.7%)	3 (6.8%)	8 (7.0%)	6 (5.2%)	14 (6.1%)	17 (6.2%)
Headache	5 (4.3%)	1 (2.3%)	7 (6.1%)	9 (7.8%)	16 (7.0%)	17 (6.2%)
Influenza	5 (4.3%)	1 (2.3%)	6 (5.2%)	6 (5.2%)	12 (5.2%)	13 (4.7%)
Arthralgia	4 (3.4%)	0	6 (5.2%)	5 (4.3%)	11 (4.8%)	11 (4.0%)
Nasopharyngitis	6 (5.1%)	3 (6.8%)	8 (7.0%)	0	8 (3.5%)	11 (4.0%)
Pyrexia	9 (7.7%)	2 (4.5%)	3 (2.6%)	6 (5.2%)	9 (3.9%)	11 (4.0%)
Anaemia	3 (2.6%)	0	8 (7.0%)	2 (1.7%)	10 (4.3%)	10 (3.6%)
Diarrhoea	3 (2.6%)	0	6 (5.2%)	4 (3.5%)	10 (4.3%)	10 (3.6%)
Gastroenteritis	1 (0.9%)	2 (4.5%)	4 (3.5%)	2 (1.7%)	6 (2.6%)	8 (2.9%)
Fatigue	0	0	3 (2.6%)	4 (3.5%)	7 (3.0%)	7 (2.6%)
Tonsillitis	0	0	5 (4.3%)	1 (0.9%)	6 (2.6%)	6 (2.2%)
Vomiting	4 (3.4%)	0	1 (0.9%)	5 (4.3%)	6 (2.6%)	6 (2.2%)
Abdominal pain upper	1 (0.9%)	0	4 (3.5%)	1 (0.9%)	5 (2.2%)	5 (1.8%)
Aspartate aminotransferase increased	4 (3.4%)	1 (2.3%)	2 (1.7%)	2 (1.7%)	4 (1.7%)	5 (1.8%)
Back pain	2 (1.7%)	2 (4.5%)	1 (0.9%)	1 (0.9%)	2 (0.9%)	4 (1.5%)
Folliculitis	0	0	0	4 (3.5%)	4 (1.7%)	4 (1.5%)
Pruritus	0	0	0	4 (3.5%)	4 (1.7%)	4 (1.5%)
White blood cell count decreased	1 (0.9%)	0	0	4 (3.5%)	4 (1.7%)	4 (1.5%)

Key: MedDRA= Medical Dictionary for Regulatory Activities
[a] Includes all placebo subjects excluding data after a subject is rescued with guselkumab.
[b] Includes placebo subjects who were rescued with guselkumab. Data in this group occurred after a subject crossed over to guselkumab.
Note: Subjects are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 26.0.

Treatment-emergent AEs by SOC and PT- Pooled data

Placebo-controlled induction period

In the GALAXI studies, 46.8% of participants in the guselkumab 200 mg IV group and 51.7% of participants in the placebo IV group had treatment-emergent AEs. In GRAVITI, 46.1% of participants in the guselkumab 400 mg SC group and 49.6% of participants in the placebo SC group had treatment-emergent AEs.

The SOCs with the highest overall frequencies of treatment-emergent AEs were:

- Infections and infestations: the most frequently reported PTs in the CD combined guselkumab and placebo treatment groups were COVID-19 (3.2% and 3.7% of participants, respectively) and upper respiratory tract infection (2.8% and 4.3% of participants, respectively).
- Gastrointestinal disorders: the most frequently reported PTs in the CD combined guselkumab and placebo treatment groups were abdominal pain (2.1% and 4.0% of participants, respectively) and Crohn's disease (2.1% and 7.9% of participants, respectively).

Through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks))

The SOCs with the highest number of treatment-emergent AEs per 100 subject-years were:

- Infections and infestations: The PTs with the highest number per 100 subject-years in the CD combined guselkumab and placebo treatment groups were COVID-19 (14.04 and 12.52 per 100 subject-years, respectively) and upper respiratory tract infection (12.76 and 16.44 per 100 subject-years, respectively).
- Gastrointestinal disorders: The PTs with the highest number per 100 subject-years in the CD combined guselkumab and placebo treatment groups were Crohn's disease (10.08 and 42.27 per 100 subject-years, respectively) and abdominal pain (8.93 and 12.52 per 100 subject-years, respectively).

Serious adverse event/deaths/other significant events

Deaths

One death of a guselkumab-treated participant was reported in the CD studies. The death attributed to a gunshot wound (i.e. non-suicidal) was reported before Week 12 in a participant in the 400 mg SC → 100 mg SC q8w group in GRAVITI study and was considered not related to study intervention by the investigator.

SAEs

Placebo-controlled Induction Period

The proportions of participants with SAEs were:

- In GALAXI studies, 2.9% of participants in the guselkumab 200 mg IV group and 6.2% of participants in the placebo IV group.
- In GRAVITI study, 2.2% of participants in the guselkumab 400 mg SC group and 7.7% of participants in the placebo SC group.

The SOC with the highest overall frequencies of SAEs was Gastrointestinal disorders: the most frequently reported PT in the CD combined guselkumab and placebo treatment groups was CD (0.6% and 2.7% of participants, respectively).

Through The Reporting Period Up to Approximately 1 Year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks))

The number of SAEs per 100 subject-years was:

- In GALAXI studies through Week 48, 9.83 and 14.43 in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 18.34 in the ustekinumab group, and 35.91 per 100 subject-years in the placebo group.
- In GRAVITI study through Week 24, 16.94 and 13.17 in the guselkumab 400 mg SC → 200 mg SC q4w and 400 mg SC → 100 mg SC q8w groups, respectively, and 36.19 per 100 subject-years in the placebo group.

The SOC with the highest number of SAEs per 100 subject-years was gastrointestinal disorders: the PT with the highest number per 100 subject-years in the CD combined guselkumab and placebo treatment groups was Crohn's disease (1.53 and 14.09 per 100 subject-years, respectively).

A patient treated with guselkumab 1200 mg IV experienced acute pancreatitis during the maintenance phase of GALAXI 1 study (200 mg SC q4w). The event occurred at Day 252 of study drug administration, it was considered moderate and not related to study drug.

Angina unstable was reported with onset on Study Week 29 in a participant with preexisting CV risk factors of hyperlipidemia and hypertension in the guselkumab 200 mg IV → guselkumab 200 mg SC q4w group of GALAXI 2 study.

Coronary artery disease was reported with onset on Study Day 291/Week 42 in a participant with preexisting risk CV factors of angina pectoris, coronary artery disease, and hypertension in the guselkumab 200 mg IV → guselkumab 100 mg SC q8w group of GALAXI 2 study.

Adverse events of interest/special interest

Active tuberculosis (TB) and malignancies were defined as adverse events of special interest by the Applicant across the GALAXI and GRAVITI studies. Opportunistic infections, anaphylactic and serum sickness reactions, MACE, VTE and Clinically important hepatic disorders were defined as AEs of interest. Suicidal intent and behaviour were also followed throughout the CD studies.

Active TB

One case of nonserious extrapulmonary active TB was reported during maintenance (Study Day 99, GALAXI 3 study), in the 200 mg IV → 100 mg SC q8w group in a participant (who had tested negative for latent TB at screening) from an endemic region, leading to discontinuation of study intervention.

The patient was enrolled and subsequently randomly assigned to receive treatment with guselkumab 200 mg iv and was stratified to the BIO-FAIL cohort. No medical history was reported. Concomitant medication reported at study entry for CD included mesalazine and prednisolone. It was noted that the central laboratory failed to provide a result on the QFT screening samples twice during screening due to a validation issue. On the third QFT sample collection (one month before first induction dose of guselkumab 200 mg) the screening QFT Tuberculosis (TB) test performed by the central lab was negative. and there was no reported history of previous contact with anyone having TB. On an unknown date, the participant complained of abdominal pain and at Study Day 97/Week 14 an abdominal ultrasound revealed a few enlarged nodes in the para-aortic and portal hepatic regions. There was also extensive neck lymphadenopathy with internal necrosis/caseation/early abscess formation noted. At Study Day 99/ Week 14, after the Study Day 89/Week 12 dose of study intervention, a real time polymerase chain reaction test detected *Mycobacterium tuberculosis* complex and the participant was diagnosed with active tuberculosis. This event was determined to be non serious. The investigator considered the event of tuberculosis to be doubtfully related to the study intervention. On the same day (Study Day 99/Week 14), a lymph node biopsy showed granulomatous inflammation and areas of necrosis including caseous necrosis compatible for tuberculosis. The study intervention was permanently discontinued, with the last dose received on Study Day 89/Week 12. The participant received treatment with ethambutol dihydrochloride/isoniazid/pyrazinamide/rifampicin. At the time of discontinuation from the study, the event of tuberculosis was reported as resolving.

Malignancies

No malignancies were reported during the placebo-controlled induction period of the GALAXI studies and GRAVITI study.

Through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)), malignancies were reported in 2 guselkumab-treated participants:

- follicular thyroid carcinoma reported during maintenance (Study Day 101), in the 200 mg IV → 200 mg SC q4w group led to discontinuation of study intervention (GALAXI 3 study).

On Study Day 101/Week 14, after the Study Day 85/Week 12 dose of study intervention, the participant developed the event of follicular thyroid cancer of severe intensity. This event was determined to be serious. The investigator considered this event to be not related to the study

intervention. There was a history of neck swelling. *On Study Day 175/Week 25, the participant was hospitalized* and right hemithyroidectomy was performed. Histological results showed minimally invasive follicular carcinoma of the thyroid gland. TNM stage: pT3a, L0 V0 Pn0; Resection status: R0. On Study Day 177/Week 25, left residual thyroidectomy was performed. Histological results showed minimally invasive follicular carcinoma of the thyroid. Nodular goiter with mixed follicular thyroid adenoma localized at circumscribed area, but without evidence of infiltration from the clinically suspected follicular thyroid carcinoma.

- basal cell carcinoma reported during maintenance (Study Day 281), in the 600 mg IV → 200 mg SC q4w group (GALAXI 1 study).

A nonserious event of basal cell carcinoma (reported term: basal cell carcinoma on the skin of the neck), of mild intensity, was reported. The lesion was removed completely and the event was reported as resolved on the same day.

An additional malignancy was reported in the CD All Treated Phase 2/3 Analysis Set: a prostate cancer reported during maintenance (Study Day 152), in the guselkumab 1200 mg IV → 200 mg SC q4w group of Study GALAXI 1. This event was confirmed via a prostate biopsy. The participant had a prostate-specific antigen (PSA) value of 4.7 ng/mL (normal range [NR] ≤4 ng/mL) before the study participation. A magnetic resonance imaging (MRI) scan showed a T2 hypointense nodule in the right central zone. Study intervention was permanently discontinued and the participant was withdrawn from the study due to this event. The event was reported as resolving at the time of this report. After further investigation, it was determined by the investigator that the prostate cancer event was not related to study intervention.

In the Week 48 CSR of the GRAVITI study submitted during the procedure, one malignancy (basal cell carcinoma) was reported in a participant in the guselkumab 100 mg SC q8w treatment group through Week 48. The skin lesion was excised, and the investigator assessed the AE as resolved and not related to study intervention. The participant continued study intervention.

Other AEs of interest

Opportunistic infections

Of the 5 opportunistic infections reported through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)), 3 occurred in the guselkumab treatment groups: one nonserious case of oesophageal candidiasis and one nonserious case of CMV infection (IgM positive, PCR negative) occurred during the placebo-controlled induction period, in the guselkumab 200 mg IV group in GALAXI 3. These 2 events resolved and did not lead to study treatment discontinuation. The aforementioned case of active TB was reported in the guselkumab 200 mg IV → 100 mg SC q8w group in GALAXI 3.

Anaphylaxis and Serum Sickness Reactions

There were no reports of anaphylaxis or serum sickness reactions in the guselkumab treatment groups of GALAXI and GRAVITI studies.

MACE

No MACE was reported during the placebo-controlled induction period.

Through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)), MACE (PT: ischemic stroke; serious) was reported in GALAXI 2 study in one participant in the guselkumab 200 mg IV → 100 mg SC q8w group with pre-existing cardiovascular risk factors.

An additional MACE (PT: myocardial infarction; nonserious) was reported in the CD All Treated Phase 2/3 Analysis Set in a participant of GALAXI 1 study in the guselkumab 600 mg IV → 200 mg SC q4w group during concurrent events of Wernicke's encephalopathy and septic shock.

VTE

No VTEs were reported among participants who received 200 mg IV or 400 mg SC induction and went on to guselkumab maintenance treatment.

During the placebo-controlled induction period, 2 VTEs were reported in guselkumab-treated participants who both had risk factors for VTE: 1 pulmonary embolism in the 1200 mg IV group and 1 deep venous thrombosis in the 600 mg IV group, both events were reported in the GALAXI 1 study.

No additional VTEs were observed through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)).

During the placebo-controlled induction period of GALAXI 2 study, 1 VTE (deep vein thrombosis and pulmonary embolism) was reported in the ustekinumab group, in a participant without known thromboembolic risk factors.

An SAE of portal vein thrombosis, which was not identified in the prespecified analysis for VTE because the PT was not included in the search methodology, was reported in GRAVITI study through Week 48 in a participant in the guselkumab 200 mg SC q4w treatment group with a medical history and recurrent treatment-emergent AEs of pancreatitis. The AE of portal vein thrombosis was assessed as not related to study intervention by the investigator

Clinically Important Hepatic Disorders

Placebo-controlled induction:

- In GALAXI 2 study, one participant in the guselkumab 200 mg IV treatment group, with an SAE of hepatic disorder (met biochemical criteria for Hy's law). Dosing was interrupted. The participant had normal LFTs at baseline. The highest ALT and AST elevations were 2.2 and 3.6xULN, respectively, and were transient, and the participant resumed guselkumab treatment at Study Week 20, after normalization of LFTs. The participant was subsequently diagnosed with Gilbert's disease. Other potential risk factors were macrogol administered in preparation for ileocolonoscopy and a recent workout.
- In GALAXI 1 study, a SAE of 'toxic hepatitis' was reported in a participant who received guselkumab 1200 mg IV induction at Study Weeks 0, 4 and 8 and 200 mg SC at Study Week 12. Following normal LFTs at baseline, the pre-dosing LFTs prior to the Study Week 12 SC dose met the biochemical criteria for Hy's law. The ALT or AST ≥8xULN threshold was also reached. The SAE led to discontinuation of study intervention and resolved. The case was confounded by an enterovirus infection AE (clinical diagnosis, no confirmatory testing) reported prior to LFT elevations.
- In GALAXI 3 study, a participant receiving guselkumab 200 mg IV induction had a reported AE of hepatic enzyme increased. The ALT or AST ≥5xULN and ALP ≥2xULN thresholds were reached at Study Week 8, the following days ALT and AST increased to ≥8xULN leading to discontinuation of study intervention, after which the LFTs normalized. The case was confounded by recent initiation of treatment for latent TB (isoniazid) and a concurrent AE of CMV infection (IgM positive and PCR negative).
- In GRAVITI study, a participant receiving guselkumab 400 mg SC induction had a reported AE of ALT increased. The participant had a medical history of abnormal liver enzymes with an ALT

of 1.6xULN at screening and had a subsequent elevation of ALT ≥5xULN and ALP ≥2xULN at Study Week 0/Study Day 1, prior to the first and only dose. Due to the persistently elevated ALT values the participant did not receive study intervention at Study Week 4 or Week 8 and was subsequently discontinued from the study per the protocol at Study Week 8, after the liver test abnormalities resolved. The case was confounded by concomitant medication (fluconazole).

Maintenance period (Week 12 to Week 48 for GALAXI studies and Week 12 to Week 24 for GRAVITI):

- One event occurred in GALAXI 3 study, a SAE of DILI was reported in a participant in guselkumab 200 mg IV → 100 mg SC q8w treatment group. The ALT or AST ≥3xULN and total bilirubin ≥2xULN thresholds were both reached within 24 hours of each other (not at the same time point). The total bilirubin peaked first followed by the peak in ALT and AST while the total bilirubin was decreasing. This case was confounded by a recent COVID-19 vaccination, CD flare, possible viral illness, and treatment with multiple antibiotics (piperacillin/tazobactam, vancomycin, cefepime, metronidazole).
- In GALAXI 1 study, an AE of hepatic enzyme increased was reported in a participant in guselkumab 200 mg IV → 100 mg SC q8w treatment group. At Study Week 24, transaminase values were ALT 4xULN and AST 1.5xULN without total bilirubin elevation. At baseline ALT was 4.4xULN and AST was 2.1xULN suggesting an underlying liver disease prior to first dose of study intervention.
- In GALAXI 2 study, an AE of abnormal hepatic function was reported in a participant in the guselkumab 200 mg IV → 100 mg SC q8w group. The ALT or AST ≥ 3xULN threshold was reached at Study Week 32. This event led to discontinuation of study intervention after which LFTs normalized. A concurrent AE of fatty liver disease was reported.
- 1 participant in the ustekinumab treatment group had an AE of "International normalised ratio", leading to discontinuation of study intervention.
- 1 participant in the placebo treatment group had an AE of "hepatic enzyme increased", leading to discontinuation of study intervention.

Hepatic disorder AEs

For the CD Safety Phase 2/3 Analysis Set, the number of hepatic disorder AEs per 100 subject-years was similar between the guselkumab treatment group and placebo groups in the pooled CD studies (8.17 and 7.83 per 100 subject-years, respectively, through the reporting period up to approximately 1 year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)). The SOC with the highest overall number of hepatic disorder AEs per 100 subject-years was Investigations and the most commonly reported PTs in this SOC were alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased.

Table 68: Number of Subjects With Select Treatment-emergent Hepatic Disorder Adverse Events During Placebo-controlled Period (Week 0 to Week 12) by System Organ Class and Preferred Term; CD Safety, Phase 2/3 Studies Analysis Set

	GALAXI 1, 2, 3[a]		GRAVITI[a]		CD Combined[a]	
	Placebo	GUS 200 mg IV q4w	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]
Analysis set: CD Safety, Phase 2/3 Studies	211	649	117	230	328	879
Average duration of follow-up (weeks)	12.2	12.3	12.0	12.3	12.1	12.3
Average exposure (number of administrations)	2.9	2.9	2.9	3.0	2.9	3.0
Subjects with 1 or more select hepatic disorder adverse events	2 (0.9%)	13 (2.0%)	0	2 (0.9%)	2 (0.6%)	15 (1.7%)
System organ class Preferred term						
Investigations	2 (0.9%)	13 (2.0%)	0	2 (0.9%)	2 (0.6%)	15 (1.7%)
Alanine aminotransferase increased	1 (0.5%)	7 (1.1%)	0	1 (0.4%)	1 (0.3%)	8 (0.9%)
Aspartate aminotransferase increased	0	4 (0.6%)	0	1 (0.4%)	0	5 (0.6%)
Hepatic enzyme increased	0	4 (0.6%)	0	0	0	4 (0.5%)
Liver function test increased	0	1 (0.2%)	0	0	0	1 (0.1%)
Transaminases increased	1 (0.5%)	0	0	1 (0.4%)	1 (0.3%)	1 (0.1%)

[a] CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3; CNTO1959CRD3004 GRAVITI.
[b] Includes subjects randomized to GUS 200 mg IV (GALAXI) or GUS 400 mg SC (GRAVITI).
Note: Includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].
Note: Only the following preferred terms are included: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, hypertransaminasaemia, liver function test abnormal, hepatic function abnormal, liver function test increased.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-48 weeks)), adverse events of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, hepatic function abnormal, and liver function test increased) were reported in 3.4% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Suicidal Ideation, Suicidal Behavior, or Self-Injurious Behavior

There were no completed suicide events and no discontinuations due to suicidal ideation, behaviour, or self-injurious behaviour.

Two events of suicidal ideations or behaviour with suicidal intent were reported, 1 in a participant in the guselkumab 1200 mg IV group in GALAXI 1, and 1 in a participant in the guselkumab 200 mg SC q4w group in GALAXI 3. These events resolved. Both participants had a history of depression and suicidal ideation.

Laboratory findings

Haematology

Placebo-controlled Induction Period – Pooled CD Studies

Through Week 12, the proportions of participants with haematology laboratory (haemoglobin, lymphocyte, neutrophil, and total WBC counts) abnormalities by maximum post-baseline toxicity grades were similar between the guselkumab 200 mg IV and the placebo IV group in the GALAXI studies and between the guselkumab 400 mg SC and the placebo SC group in the GRAVITI study. Most post-baseline abnormal hematology laboratory values were Grade 1 or Grade 2. Few post-baseline Grade 3 and Grade 4 hematology toxicities were reported and are summarized hereafter:

- Haemoglobin decreased (Grade 3) was reported in 8 (1.2%) of participants in the guselkumab 200 mg IV group and 7 (3.4%) in the placebo IV group; no Grade 3 events were reported for the guselkumab 400 mg SC group and 1 (0.9%) in the placebo SC group.
- Total WBC count decreased (Grade 3) was reported in 2 (0.3%) participants in the guselkumab 200 mg IV group and no participants in the placebo IV group; no Grade 3 events were reported for the guselkumab 400 mg SC and placebo SC groups.
- Lymphocytes decreased (Grade 3) was reported in 32 (5.0%) participants in the guselkumab 200 mg IV group and 9 (4.3%) in the placebo IV group; 7 (3.1%) were reported in the guselkumab 400 mg SC group and 4 (3.5%) in the placebo SC group.
- 2 (0.3%) lymphocytes decreased Grade 4 events were reported for participants in the guselkumab 200 mg IV group and none in the placebo IV group, no Grade 4 events were reported in the guselkumab 400 mg SC and the placebo SC groups.
- Neutrophils decreased (Grade 3) was reported in 2 (0.3%) participants in the guselkumab 200 mg IV group and none in the placebo IV group; no Grade 3 events were reported in the guselkumab 400 mg SC and placebo SC groups.
- 1 (0.2%) neutrophils decreased Grade 4 event was reported in the guselkumab 200 mg IV group and none in the placebo IV group; no Grade 4 events were reported in the guselkumab 400 mg SC and placebo SC groups.

The majority of Grade 3 and 4 abnormalities were transient and did not lead to discontinuation of study intervention.

Through the Reporting Period up to Approximately 1 Year - Pooled CD Studies (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)

Through the reporting period up to approximately 1 year, the proportions of participants with hematology laboratory abnormalities by maximum post-baseline toxicity grades were similar across treatment groups Most post-baseline abnormal haematology laboratory values were Grade 1 or Grade 2. Few post-baseline Grade 3 and Grade 4 hematology toxicities were reported and are summarized below for the GALAXI studies (the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, the ustekinumab group, and the placebo group through Week 48), and

for the GRAVITI study (the guselkumab 400 mg SC → 200 mg SC q4w and 400 mg SC → 100 mg SC q8w groups and the placebo group through Week 24):

- Haemoglobin decreased of Grade 3 were reported in 7 (2.4%) and 8 (2.3%) participants in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 7 (2.0%) participants in the ustekinumab group and 7 (3.4%) participants in the placebo group through Week 48. Hemoglobin decreased of Grade 3 were reported in 0 and 1 (0.9%) participant in the 400 mg SC → 200 mg SC q4w and 400 mg SC → 100 mg SC q8w groups, respectively, and 1 (0.9%) participant in the placebo group through Week 24.
- Total WBC count decreased of Grade 3 were reported in 2 (0.7%) and 1 (0.3%) participants in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 1 (0.3%) participant in the ustekinumab group and none in placebo group or the GRAVITI study.
- Lymphocytes decreased of Grade 3 were reported in 26 (8.8%) and 15 (4.3%) participants in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 20 (5.6%) participants in the ustekinumab group and 11 (5.3%) participants in the placebo group through Week 48. Lymphocytes decreased of Grade 3 were reported in 4 (3.5%) and 5 (4.3%) participants in the 400 mg SC → 200 mg SC q4w and 400 mg SC → 100 mg SC q8w groups, respectively, and 4 (3.5%) participants in the placebo group through Week 24
- Lymphocytes decreased of Grade 4 were reported in 1 (0.3%) and 1 (0.3%) participant in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 3 (0.8%) participants in the ustekinumab group and none in placebo group or the GRAVITI study.
- Neutrophils decreased of Grade 3 were reported in 1 (0.3%) and 3 (0.9%) participants in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 1 (0.3%) participant in the ustekinumab group and 0 participants in the placebo group through Week 48. None were in the 400 mg SC → 200 mg SC q4w, 400 mg SC → 100 mg SC q8w, and placebo treatment groups through Week 24.
- Neutrophils decreased of Grade 4 were reported in 1 (0.3%) participant in the guselkumab 200 mg IV → 200 mg SC q4w group, and none in the other groups or the GRAVITI study.

The majority of Grade 3 and 4 cases were transient and did not lead to discontinuation of study intervention.

Chemistry

Individual Study Results for CD Studies

The proportions of participants with chemistry laboratory (ALT, AST, ALP, and total bilirubin) abnormalities by maximum post-baseline values were generally similar across the guselkumab, ustekinumab, and placebo treatment groups in GALAXI 1, 2, 3 studies and between the guselkumab and placebo treatment groups in GRAVITI study.

Two cases meeting the biochemical criteria for Hy's law were reported in the CD studies. One case occurred in the guselkumab 200 mg IV treatment group during the placebo-controlled induction period and 1 occurred in the guselkumab 1200 mg IV → 200 mg SC q4w treatment group, respectively. These cases are described under *Clinically important hepatic disorders*.

Placebo-controlled Induction Period – Pooled CD Studies

Line plots of mean changes from baseline of ALT, AST, total bilirubin and ALP levels for the pooled CD studies through Week 12 did not reveal a pattern suggesting a clinically meaningful effect of guselkumab on any of the laboratory parameters evaluated.

The trends in post-baseline maximum LFT values observed were similar between the individual CD studies.

A summary of Maximum Post-baseline Liver Test Values is provided Table 69.

Table 69: Summary of Maximum Post-baseline Liver Test Values During Placebo-controlled Induction Period (Week 0 to Week 12); CD Safety, Phase 2/3 Studies Analysis Set

	GALAXI 1, 2, 3[a]						GRAVITI[a]		CD Combined[a]	
		Guselkumab								
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w	All GUS[b]	UST	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]
Analysis set: CD Safety, Phase 2/3 Studies	211	649	65	65	779	359	117	230	328	1009
Average duration of follow-up (weeks)	12.2	12.3	11.9	11.7	12.3	12.3	12.0	12.3	12.1	12.3
ALT										
Subjects with at least 1 post-baseline ALT value	209	645	65	63	773	355	114	230	323	1003
Maximum post-baseline										
≤ULN	192 (91.9%)	562 (87.1%)	61 (93.8%)	49 (77.8%)	672 (86.9%)	332 (93.5%)	108 (94.7%)	205 (89.1%)	300 (92.9%)	877 (87.4%)
>ULN	17 (8.1%)	83 (12.9%)	4 (6.2%)	14 (22.2%)	101 (13.1%)	23 (6.5%)	6 (5.3%)	25 (10.9%)	23 (7.1%)	126 (12.6%)
>1 to <3 x ULN	15 (7.2%)	79 (12.2%)	4 (6.2%)	14 (22.2%)	97 (12.5%)	22 (6.2%)	6 (5.3%)	23 (10.0%)	21 (6.5%)	120 (12.0%)
≥3 to <5 x ULN	2 (1.0%)	2 (0.3%)	0	0	2 (0.3%)	1 (0.3%)	0	1 (0.4%)	2 (0.6%)	3 (0.3%)
≥5 to <8 x ULN	0	1 (0.2%)	0	0	1 (0.1%)	0	0	1 (0.4%)	0	2 (0.2%)
≥8 x ULN	0	1 (0.2%)	0	0	1 (0.1%)	0	0	0	0	1 (0.1%)
AST										
Subjects with at least 1 post-baseline AST value	208	645	65	63	773	355	114	230	322	1003
Maximum post-baseline										
≤ULN	195 (93.8%)	578 (89.6%)	60 (92.3%)	56 (88.9%)	694 (89.8%)	330 (93.0%)	111 (97.4%)	214 (93.0%)	306 (95.0%)	908 (90.5%)
>ULN	13 (6.3%)	67 (10.4%)	5 (7.7%)	7 (11.1%)	79 (10.2%)	25 (7.0%)	3 (2.6%)	16 (7.0%)	16 (5.0%)	95 (9.5%)
>1 to <3 x ULN	13 (6.3%)	62 (9.6%)	5 (7.7%)	7 (11.1%)	74 (9.6%)	22 (6.2%)	3 (2.6%)	16 (7.0%)	16 (5.0%)	90 (9.0%)
≥3 to <5 x ULN	0	4 (0.6%)	0	0	4 (0.5%)	3 (0.8%)	0	0	0	4 (0.4%)
≥5 to <8 x ULN	0	0	0	0	0	0	0	0	0	0
≥8 x ULN	0	1 (0.2%)	0	0	1 (0.1%)	0	0	0	0	1 (0.1%)

	GALAXI 1, 2, 3[a]						GRAVITI[a]		CD Combined[a]	
		Guselkumab								
	Placebo	200 mg IV q4w	600 mg IV q4w	1200 mg IV q4w	All GUS[b]	UST	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]
Total bilirubin										
Subjects with at least 1 post-baseline total bilirubin value	209	645	65	63	773	355	114	230	323	1003
Maximum post-baseline										
≤ULN	196 (93.8%)	615 (95.3%)	60 (92.3%)	60 (95.2%)	735 (95.1%)	333 (93.8%)	112 (98.2%)	211 (91.7%)	308 (95.4%)	946 (94.3%)
>ULN	13 (6.2%)	30 (4.7%)	5 (7.7%)	3 (4.8%)	38 (4.9%)	22 (6.2%)	2 (1.8%)	19 (8.3%)	15 (4.6%)	57 (5.7%)
>1 to <2 x ULN	13 (6.2%)	24 (3.7%)	4 (6.2%)	3 (4.8%)	31 (4.0%)	17 (4.8%)	1 (0.9%)	15 (6.5%)	14 (4.3%)	46 (4.6%)
≥2 x ULN	0	6 (0.9%)	1 (1.5%)	0	7 (0.9%)	5 (1.4%)	1 (0.9%)	4 (1.7%)	1 (0.3%)	11 (1.1%)
Alkaline phosphatase										
Subjects with at least 1 post-baseline alkaline phosphatase value	209	645	65	63	773	355	114	230	323	1003
Maximum post-baseline										
≤ULN	197 (94.3%)	603 (93.5%)	63 (96.9%)	53 (84.1%)	719 (93.0%)	338 (95.2%)	100 (87.7%)	197 (85.7%)	297 (92.0%)	916 (91.3%)
>ULN	12 (5.7%)	42 (6.5%)	2 (3.1%)	10 (15.9%)	54 (7.0%)	17 (4.8%)	14 (12.3%)	33 (14.3%)	26 (8.0%)	87 (8.7%)
>1 to <2 x ULN	10 (4.8%)	40 (6.2%)	2 (3.1%)	9 (14.3%)	51 (6.6%)	17 (4.8%)	12 (10.5%)	31 (13.5%)	22 (6.8%)	82 (8.2%)
≥2 to <4 x ULN	2 (1.0%)	1 (0.2%)	0	1 (1.6%)	2 (0.3%)	0	2 (1.8%)	2 (0.9%)	4 (1.2%)	4 (0.4%)
≥4 x ULN	0	1 (0.2%)	0	0	1 (0.1%)	0	0	0	0	1 (0.1%)

Key: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal.
[a] CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3; CNTO1959CRD3004 GRAVITI.
[b] Subjects not randomized to guselkumab who inadvertently received at least one dose of guselkumab are included in the All GUS column for GALAXI studies. Subjects randomized to guselkumab who received an incorrect treatment of ustekinumab are included in their randomized treatment columns.
[c] Criteria were met if the total bilirubin of at least 2 x ULN was measured at the time of or up to 5 days after the ALT or AST at least 3 x ULN threshold was measured.
Note: Includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].
Note: The maximum post-baseline value is used to determine the category.

Through the Reporting Period up to Approximately 1 Year - Pooled CD Studies (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-48 weeks)

The majority of guselkumab-treated participants had maximum post-baseline ALT, AST, total bilirubin, and ALP levels that were within the reference range (≤1xULN).

Of the participants with abnormal post-baseline LFTs, most had mild elevations (>1 and <2xULN). In most cases, the increases in LFTs were transient and did not lead to discontinuation of study intervention.

A summary of maximum post-baseline liver test values is provided in Table 70.

Table 70: Summary of Maximum Post-baseline ALT and AST Values Through Reporting Period up to Approximately One Year; CD Safety, Phase 2/3 Studies Analysis Set

	GALAXI 1, 2, 3 (0-48 weeks)[a,b]			GRAVITI (0-48 weeks)[a,c]			CD Combined[a,b,c]		
		Guselkumab			Guselkumab			Guselkumab	
	Placebo	200 mg IV q4w → 100 mg SC q8w	200 mg IV q4w → 200 mg SC q4w	Placebo	400 mg SC q4w → 100 mg SC q8w	400 mg SC q4w → 200 mg SC q4w	Placebo	100 mg SC q8w	200 mg SC q4w
Analysis set: CD Safety, Phase 2/3 Studies	211	353	296	117	115	115	328	468	411
Average duration of follow-up (weeks)	20.7	45.1	46.6	30.0	47.0	48.0	24.0	45.5	47.0
ALT									
Subjects with at least 1 post-baseline ALT value	209	351	294	114	115	115	323	466	409
Maximum post-baseline									
≤ULN	189 (90.4%)	266 (75.8%)	230 (78.2%)	98 (86.0%)	93 (80.9%)	96 (83.5%)	287 (88.9%)	359 (77.0%)	326 (79.7%)
>ULN	20 (9.6%)	85 (24.2%)	64 (21.8%)	16 (14.0%)	22 (19.1%)	19 (16.5%)	36 (11.1%)	107 (23.0%)	83 (20.3%)
>1 to <3 x ULN	17 (8.1%)	78 (22.2%)	59 (20.1%)	14 (12.3%)	21 (18.3%)	16 (13.9%)	31 (9.6%)	99 (21.2%)	75 (18.3%)
≥3 x ULN	3 (1.4%)	7 (2.0%)	5 (1.7%)	2 (1.8%)	1 (0.9%)	3 (2.6%)	5 (1.5%)	8 (1.7%)	8 (2.0%)
AST									
Subjects with at least 1 post-baseline AST value	208	351	294	114	115	115	322	466	409
Maximum post-baseline									
≤ULN	191 (91.8%)	276 (78.6%)	236 (80.3%)	104 (91.2%)	92 (80.0%)	94 (81.7%)	295 (91.6%)	368 (79.0%)	330 (80.7%)
>ULN	17 (8.2%)	75 (21.4%)	58 (19.7%)	10 (8.8%)	23 (20.0%)	21 (18.3%)	27 (8.4%)	98 (21.0%)	79 (19.3%)
>1 to <3 x ULN	16 (7.7%)	70 (19.9%)	53 (18.0%)	8 (7.0%)	22 (19.1%)	19 (16.5%)	24 (7.5%)	92 (19.7%)	72 (17.6%)
≥3 x ULN	1 (0.5%)	5 (1.4%)	5 (1.7%)	2 (1.8%)	1 (0.9%)	2 (1.7%)	3 (0.9%)	6 (1.3%)	7 (1.7%)
ALT or AST									
Subjects with at least 1 post-baseline ALT or AST value	209	351	294	114	115	115	323	466	409
Maximum post-baseline									
≤ULN[d]	185 (88.5%)	250 (71.2%)	219 (74.5%)	97 (85.1%)	85 (73.9%)	89 (77.4%)	282 (87.3%)	335 (71.9%)	308 (75.3%)
>ULN	24 (11.5%)	101 (28.8%)	75 (25.5%)	17 (14.9%)	30 (26.1%)	26 (22.6%)	41 (12.7%)	131 (28.1%)	101 (24.7%)
>1 to <3 x ULN	21 (10.0%)	91 (25.9%)	68 (23.1%)	14 (12.3%)	28 (24.3%)	22 (19.1%)	35 (10.8%)	119 (25.5%)	90 (22.0%)
≥3 x ULN	3 (1.4%)	10 (2.8%)	7 (2.4%)	3 (2.6%)	2 (1.7%)	4 (3.5%)	6 (1.9%)	12 (2.6%)	11 (2.7%)

Key: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal.
[a] Crohn's disease: (0-48 weeks) CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3, and CNTO1959CRD3004 GRAVITI.
[b] One subject randomized to placebo inadvertently received guselkumab in maintenance; events that occurred after Week 12 are not included in this table.
[c] Subjects randomized to placebo could rescue with guselkumab during maintenance. Events that occurred after rescue with guselkumab are not included in this table.
[d] All post-baseline ALT and AST values are below their upper limit of normal.
Note: Includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].
Note: The maximum post-baseline value is used to determine the category.

Injection-site reactions

Through the reporting period up to approximately 1 year, the proportions of participants with injection-site reactions to active study agent were as follows in the GALAXI 1, 2, and 3 and GRAVITI studies:

- Through Week 48 of the GALAXI studies:
  - 4.1% of participants (0.8% of injections) in the guselkumab 200 mg IV → 200 mg SC q4w group (1 reaction led to discontinuation of study intervention [PT: injection site hypersensitivity]).
  - 1.4% of participants (0.6% of injections) in the guselkumab 200 mg IV → 100 mg SC q8w group.
  - 0.2% of participants (1 injection) in the ustekinumab group.
- Through Week 48 of the GRAVITI study:
  - Participants with 1 or more guselkumab injection-site reactions: 7.0% in the 200 mg SC q4w treatment group, 4.3% in the 100 mg SC q8w treatment group, and 2.3% in the placebo→ guselkumab group.
  - No participants in the placebo group reported injection-site reactions.

Discontinuation due to adverse events

Placebo-controlled Induction Period

The proportions of participants with treatment-emergent AEs leading to discontinuation of study intervention were:

- In GALAXI, 1.7% of participants in the guselkumab 200 mg IV group and 4.3% of participants in the placebo IV group.
- In GRAVITI, 0.4% of participants in the guselkumab 400 mg SC group and 2.6% of participants in the placebo SC group.

The most common treatment-emergent AE leading to discontinuation of study intervention was CD (0 and 2.1% of participants for the CD combined guselkumab and placebo treatment groups, respectively).

Through The Reporting Period Up to Approximately 1 Year (GALAXI 1,2,3 (0-48 weeks) and GRAVITI (0-24 weeks)

The number of treatment-emergent AEs leading to discontinuation of study intervention per 100 subject-years was:

- In GALAXI through Week 48, 7.56 and 8.20 in the guselkumab 200 mg IV → 200 mg SC q4w and 200 mg IV → 100 mg SC q8w groups, respectively, 9.01 in the ustekinumab group, and 25.14 per 100 subject-years in the placebo group.
- In GRAVITI through Week 24, 1.88 and 0.00 in the guselkumab 400 mg SC → 200 mg SC q4w and 400 mg SC → 100 mg SC q8w groups, respectively, and 18.10 per 100 subject-years in the placebo group.

The treatment-emergent AE leading to discontinuation of study intervention with the highest number per 100 subject-years was CD (1.53 and 13.31 per 100 subject-years for the CD combined guselkumab and placebo treatment groups, respectively).

Analysis of AEs of guselkumab across diseases

IBD

A summary of Treatment-emergent Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12) is provided in Table 71.

Table 71: Overall Summary of Treatment-emergent Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12); IBD Safety, Phase 3 Studies Analysis Set

	Ulcerative Colitis[a]		Crohn's Disease[a]						Inflammatory Bowel Disease[a]		
			GALAXI 2, 3		GRAVITI		CD Combined			Guselkumab	
	Placebo	GUS 200 mg IV q4w	Placebo	GUS 200 mg IV q4w	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]	COMB Placebo	COMB 200 mg IV q4w	All GUS[b]
Analysis set: IBD Safety, Phase 3 Studies	280	421	148	582	117	230	265	812	545	1003	1233
Average duration of follow-up (weeks)	11.9	12.2	12.2	12.4	12.0	12.3	12.1	12.4	12.0	12.3	12.3
Average exposure (number of administrations)	2.9	2.9	2.9	3.0	2.9	3.0	2.9	3.0	2.9	2.9	3.0

	Ulcerative Colitis[a]		Crohn's Disease[a]						Inflammatory Bowel Disease[a]		
			GALAXI 2, 3		GRAVITI		CD Combined			Guselkumab	
	Placebo	GUS 200 mg IV q4w	Placebo	GUS 200 mg IV q4w	Placebo	GUS 400 mg SC q4w	Placebo	All GUS[b]	COMB Placebo	COMB 200 mg IV q4w	All GUS[b]
Subjects who died	2 (0.7%)	1 (0.2%)	0	0	0	1 (0.4%)	0	1 (0.1%)	2 (0.4%)	1 (0.1%)	2 (0.2%)
Subjects with 1 or more:											
Adverse events	141 (50.4%)	208 (49.4%)	71 (48.0%)	274 (47.1%)	58 (49.6%)	106 (46.1%)	129 (48.7%)	380 (46.8%)	270 (49.5%)	482 (48.1%)	588 (47.7%)
Adverse events by maximum intensity[c]											
Mild	74 (26.4%)	133 (31.6%)	35 (23.6%)	166 (28.5%)	24 (20.5%)	65 (28.3%)	59 (22.3%)	231 (28.4%)	133 (24.4%)	299 (29.8%)	364 (29.5%)
Moderate	49 (17.5%)	62 (14.7%)	31 (20.9%)	89 (15.3%)	29 (24.8%)	38 (16.5%)	60 (22.6%)	127 (15.6%)	109 (20.0%)	151 (15.1%)	189 (15.3%)
Severe	18 (6.4%)	13 (3.1%)	5 (3.4%)	19 (3.3%)	5 (4.3%)	3 (1.3%)	10 (3.8%)	22 (2.7%)	28 (5.1%)	32 (3.2%)	35 (2.8%)
Serious adverse events	20 (7.1%)	12 (2.9%)	9 (6.1%)	16 (2.7%)	9 (7.7%)	5 (2.2%)	18 (6.8%)	21 (2.6%)	38 (7.0%)	28 (2.8%)	33 (2.7%)
Adverse events leading to discontinuation of study agent	11 (3.9%)	7 (1.7%)	7 (4.7%)	11 (1.9%)	3 (2.6%)	1 (0.4%)	10 (3.8%)	12 (1.5%)	21 (3.9%)	18 (1.8%)	19 (1.5%)
Infections[d]	43 (15.4%)	67 (15.9%)	26 (17.6%)	103 (17.7%)	24 (20.5%)	43 (18.7%)	50 (18.9%)	146 (18.0%)	93 (17.1%)	170 (16.9%)	213 (17.3%)
Serious infections[d]	1 (0.4%)	3 (0.7%)	0	0	0	1 (0.4%)	0	1 (0.1%)	1 (0.2%)	3 (0.3%)	4 (0.3%)

[a] Ulcerative colitis: CNTO1959UCO3001 Induction Study 2; Crohn's disease: CNTO1959CRD3001 GALAXI 2 and GALAXI 3; CNTO1959CRD3004 GRAVITI.
[b] Subjects not randomized to guselkumab who inadvertently received at least one dose of guselkumab are included in the All GUS column.
[c] The maximum severity event experienced by the subject is used.
[d] Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'.
Note: Ulcerative colitis: includes only subjects with modified Mayo score 5-9 at induction baseline; Crohn's disease: includes only subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease].

Analysis of AEs Across All Diseases (Including CD, UC, and Psoriatic Diseases)

The overall guselkumab safety profile in CD was consistent with UC and the well-characterized safety profile established in the approved plaque psoriasis and PsA indications.

Due to differences in study designs, the number and type of study intervention administrations were different in the placebo-controlled induction period of the CD and UC studies (3 IV administrations in QUASAR and GALAXI and 3 SC administrations in GRAVITI) and in the placebo-controlled period (3 to 6 SC administration) in the psoriatic diseases (psoriasis and PsA) studies. Although all maintenance regimens across the different diseases involved SC administration, dose regimens also differed among studies in the different diseases. Through the reporting period up to approximately 1 year, the mean total dose of guselkumab in the CD and UC studies was higher than the mean total dose in the psoriatic disease studies.

The duration of follow-up for participants across the disease populations varied:

- For the placebo-controlled induction period, the average duration of follow-up for guselkumab-treated participants in the IBD studies was approximately 7 weeks shorter than the duration of follow-up for psoriatic diseases.
- For data through the reporting period up to approximately 1 year, the average duration of follow-up for guselkumab-treated participants was approximately 5 weeks shorter in the CD studies compared with the UC and psoriatic diseases studies.

In addition, through the reporting period up to approximately 1 year across all disease populations, the average duration of follow-up for placebo-treated participants was shorter than in guselkumab-treated participants.

Standard AEs

For treatment-emergent AEs, SAEs, AEs leading to discontinuations of study intervention, severe AEs, infections, and serious infections, the number of participants with events per 100 subject-years was generally similar or not higher in the guselkumab-treated participants, compared with the placebo-treated participants across CD, UC, and psoriatic disease studies.

During the placebo-controlled period, regardless of treatment received (guselkumab or placebo), participants with CD and UC reported AEs at a higher rate per 100 subject-years than participants with psoriatic diseases suggesting that the higher rate of AEs was related to the underlying disease. This trend was less apparent through the reporting period up to approximately 1 year.

Targeted AEs

In the evaluation of targeted AEs, there were no findings that suggest a change in the well-characterized guselkumab safety profile. Rates of targeted AEs were similar across CD, UC, and psoriatic diseases.

Safety in special groups

Placebo-controlled Induction Period

No differences were observed in the proportions of guselkumab-treated participants compared with placebo participants with AEs, SAEs, or AEs leading to discontinuation of study intervention when evaluated according to the participants' weight, sex, race, or ethnicity. For the subgroup of ≥65 years, the proportions of participants with AEs were higher in the guselkumab treatment group (15/39 [38.5%]) compared with the placebo group (2/7 [28.6%]). Also, for the ≥65 years subgroup, the proportion of participants with infections was higher in the guselkumab treatment group (4/39 [10.3%]) compared with the placebo group (0/7 [0.0%]). The limited number of participants in this subgroup limits the interpretation of these data. No trends in infections were observed for all other demographic subgroups.

Through The Reporting Period Up to Approximately 1 Year

When compared with placebo-treated participants, no trends were observed with regards to differences in the event rates of guselkumab-treated participants for AEs, SAEs or AEs leading to discontinuation of study intervention through the reporting period up to approximately 1 year, when evaluated according to the participants' weight, sex, race or ethnicity in pooled CD studies, except for the subgroup ≥65 years in which the event rates of AEs per 100 subject years of follow-up were numerically higher in the guselkumab treatment group compared with the placebo group (324.99 and 157.27, respectively). For infections, trends for numerically higher event rates of infections per 100 subject-years of follow-up were observed in the guselkumab treatment group (n=42) compared with

the placebo group (n=7) for the small subgroup of participants ≥65 years (68.61 and 0.0, respectively). Higher event rates of infection were also observed for male participants in the guselkumab treatment group compared with the placebo group (81.20 and 63.03, respectively).

Post marketing experience

As of the data cut-off date of 12 July 2023, guselkumab was approved for psoriasis and PsA in the European Union, the United States, Japan, Canada, and many other countries worldwide. The estimated cumulative global exposure to guselkumab from launch through 30 June 2023 was 407,104 person-years.

Psoriasis

PSOLAR 2

The PSOLAR registry (Protocol C0168Z03) is an international, multicenter, prospective, observational registry for monitoring the long-term safety experience and clinical status of patients with moderate-to-severe psoriasis who are ≥18 years of age and eligible to receive or are actively receiving any systemic therapies for psoriasis. PSOLAR was initiated in 2007. In March 2018, the PSOLAR protocol was amended (PSOLAR 2) to allow enrollment of patients receiving treatment with guselkumab or an IL-17 inhibitor (eg, secukinumab, ixekizumab, brodalumab). The first patient exposed to guselkumab was enrolled into PSOLAR 2 on 14 January 2019. A total of 3,555 patients were enrolled in PSOLAR 2 cumulatively through 12 July 2023.

In the guselkumab cohort a total of 2,178 patients with psoriasis receiving or starting guselkumab were enrolled in PSOLAR 2 cumulatively through 12 July 2022. As of 12 July 2023, the on-registry exposure for patients ever-exposed to guselkumab is 4,507 patient-years with a median duration of follow-up of 2.02 years.

AEs

Rates of AEs and SAEs were calculated based on 2 definitions of exposure:

- Exposure at any time prior to the event (ever-exposed definition), and
- Exposure within a risk window of 91 days prior to the event for biologic agents (91-day exposed definition).

The cumulative unadjusted incidence rates for AEs and SAEs using the ever-exposed definition of exposure were 24.78/100 patient-year and 4.39/100 patient-years, respectively, for the guselkumab-exposed population of registry patients. The cumulative unadjusted incidence rates for AEs and SAEs using the 91-day exposure definition were 29.50/100 patient-years and 5.29/100 patient-years, respectively, for the guselkumab-exposed population of registry patients. The observed AE and SAE incidence rates for the guselkumab cohort were similar to those observed in the IL-17 exposed cohort.

Using the ever-exposed definition of exposure, the cumulative unadjusted incidence rates for reported cardiac disorders was similar for the guselkumab cohort (0.78/100 patient-years) and the IL-17 cohort (0.68/100 patient-years), while the cumulative unadjusted incidence rate for malignancy AEs were slightly numerically lower in the guselkumab cohort (1.62/100 patient-years) compared with the IL-17 cohort (1.76/100 patient-years). Using the 91-day exposure definition, the cumulative unadjusted incidence rates for infections/infestations were numerically lower in the guselkumab cohort (11.45/100 patient-years) compared with the IL-17 cohorts (13.32/100 patient-years). Given the current enrollment and short duration of follow-up for the PSOLAR 2 registry, these incidence rates should be interpreted with caution.

PsoBest

The German registry on Treatment of PsoBest (Protocol [CNTO1959PSO4001]), is a prospective observational study designed to examine the long-term safety and effectiveness of systemic therapies, including biologics, available to treat adults with moderate-to-severe plaque psoriasis or PsA in Germany. The registry started in 2008 and aimed to enroll 3,500 adult patients with psoriasis and PsA being treated for the first time or switched to a biologic or a systemic therapy from dermatological practices and clinics. The guselkumab-treated cohort in the PsoBest registry was initiated in December 2017 after guselkumab was approved for the treatment of psoriasis.

From 13 December 2017 to 31 December 2022, a total of 17,309 patients have been registered in the registry. The cumulative number of patients included in the guselkumab cohort is 1,247; mean age and duration of illness were 47.6 years and 19.2 years, respectively. The cumulative exposure years of guselkumab were 951.12 and 434.39 for the psoriasis and PsA groups respectively.

All AEs

There were 655 SAEs and 583 AEs in the PsoBest period from 13 December 2007 to 31 December 2022 in the guselkumab cohort. Among the 655 SAEs reported, the most frequently reported MedDRA PTs were in the following SOCs: Surgical and medical procedures (n=170) and Injury, poisoning and procedural complications (n=61). During this period, 17 patients exposed to guselkumab reported 25 malignancy SAEs (SOC Neoplasm benign, malignant and unspecified [incl cysts and polyps]). A total of 12 all-cause deaths were reported in the guselkumab cohort during the period from 13 December 2007 to 31 December 2022.

Pregnancy

OTIS

The Tremfya (guselkumab) Pregnancy Exposure Registry is a North American based, observational pregnancy registry designed to monitor planned or unplanned pregnancies exposed to guselkumab to treat an approved indication (psoriasis or PsA), and to collect follow-up information on the health status of the infants through approximately 1 year of age. The registry is conducted by the OTIS Research Group as an integrated project within the existing OTIS Autoimmune Diseases in Pregnancy Project, which is administered by investigators at the coordinating site located at the University of California, San Diego.

Initiated in August 2018, the registry aims to recruit 100 patients exposed to guselkumab from the United States and Canada. Through 31 May 2023, 7 patients have been enrolled. Outcomes have been collected on 4 pregnancies including 3 live born infants and 1 spontaneous abortion. No major malformations have been reported. Three pregnancy outcomes are still pending at this time.

TREMFYA Pregnancy Healthcare Database Study

Study PCSIMM001324 is an ongoing retrospective cohort study using health administrative claims databases to monitor pregnancy outcomes and link infant outcomes in women with psoriasis who were exposed to guselkumab during pregnancy. The first interim report will be available in the fourth quarter of 2025.

Long-term safety results

Upon the CHMP's request, the MAH provided an updated safety report. All clinical study related safety data provided in this Safety Update Report are from Week 152 through 15 May 2024 for GALAXI 1 or from Week 48 through 15 May 2024 for GALAXI 2, GALAXI 3, and GRAVITI. Since no formal DBL has been performed for this Safety Update Report, data which were collected during the reporting period

through 15 May 2024 in the GALAXI and GRAVITI studies, have not been thoroughly cleaned and finalized.

The Safety Update Report provided an additional 231.5 total subject-years of follow-up for GALAXI 1, 875.1 total subject-years of follow-up for GALAXI 2 and GALAXI 3, and 90.8 total subject-years of follow-up for the GRAVITI study in guselkumab-treated subjects, compared with the data provided in the initial guselkumab CD submission and in the GRAVITI Week 48 CSR.

The Updated safety report focused on Death cases and SAEs including serious infection cases, AEs leading to discontinuation, targeted AEs and suicidal ideation/behaviour-related AEs. Liver enzyme elevations satisfying Hy's law criteria as well as post-baseline ≥5x ULN ALT/AST elevations were also presented.

Three deaths (traffic accident, sudden death of a patient without known pre-existing cardiovascular risk factors, arteriosclerosis coronary artery in a participant with pre-existing cardiovascular risk factors) occurred during the reporting period in GALAXI studies. All of them were assessed as not related to study intervention. No death occurred in GRAVITI study during the reporting period.

As for serious AEs, the SAE event rates in GALAXI 1, GALAXI 2, GALAXI 3 and GRAVITI were similar across the treatment groups. Event rates of SAEs were led by Gastrointestinal disorders and Infections/infestations SOCs. Within the infections/Infestations SOC, the SAEs were led by abdominal/anal abscess SAEs.

In GALAXI studies, the most frequently reported AEs leading to discontinuation of study intervention was CD, Maternal exposure during pregnancy. Other AEs leading to discontinuation of study intervention in participants treated with guselkumab were prostate cancer, adenocarcinoma of colon and active tuberculosis. In GRAVITI study, no AEs leading to discontinuation of study intervention occurred during the reporting period.

A total of 6 malignancies occurred during the reporting period in GALAXI studies, three of them for patients on guselkumab (adenocarcinoma of colon, prostate cancer and malignant melanoma, this patient entered to the study with an existing naevus pigmentosus in GALAXI 1 study) and three for patients on ustekinumab (non-Hodgkin's lymphoma, squamous cell carcinoma of the skin and breast cancer). In GRAVITI study, no malignancies occurred during the reporting period.

One SAE of active TB was reported in GALAXI 3 in the guselkumab 200 mg IV → 200 mg SC q4w group, in a participant from an endemic region. The participant had tested negative for latent TB at screening and, at the time that TB was diagnosed, was taking concomitant oral corticosteroids and azathioprine. The event led to discontinuation of study intervention. No cases of active TB were reported in the placebo and ustekinumab groups of GALAXI studies and in the whole GRAVITI study during the reporting period.

In GALAXI studies, 4 cases of opportunistic infections occurred in guselkumab-treated participants (ophthalmic herpes zoster, esophageal candidiasis, herpes zoster reactivations, active TB discussed above) and 1 case (fungal tonsillitis) was reported in the placebo group during the reporting period. No cases of opportunistic infections occurred in the ustekinumab group during the reporting period.

In GRAVITI study, a previously reported SAE of gastroenteritis was identified as coupled to fungal esophagitis and was entered in the safety database of GRAVITI study after the 15 May 2024 cutoff.

There were no cases of anaphylaxis or serum sickness reactions in participants treated with guselkumab in the GALAXI and GRAVITI studies during the reporting period.

Two deaths due to fatal MACEs (sudden death of participant in guselkumab 200 mg SC q4w group, without known pre-existing cardiovascular risk factors, one case of arteriosclerosis coronary artery in a

participant with pre-existing cardiovascular risk factors in the ustekinumab group) were reported in GALAXI 1 and GALAXI 3 studies, respectively and assessed as not related to study intervention by investigators.

As for VTE events, 1 nonserious VTE (deep venous thrombosis) occurred in a participant in the placebo → ustekinumab → guselkumab 200 mg SC q4w group of GALAXI 3 who had risk factors for VTE. This case was assessed as not related to study intervention by the investigator.

There were no reports of anaphylaxis or serum sickness reactions.

Five clinically important hepatic disorder AEs occurred for guselkumab-treated participants during the reporting period in GALAXI studies. All 5 cases were confounded by medical history, concurrent AEs associated with hepatic disorder, concomitant medications or alcohol/cocaine abuse. None of these cases met the biochemical criteria of Hy's law. Two of the five patients discontinued due to the clinically important hepatic disorder, a third one has already been discontinued at the time of liver enzyme elevation due to active TB infection. The two remaining patients were able to remain on guselkumab treatment and their transaminase levels normalized later on. In GRAVITI study, no clinically important hepatic disorders occurred during the reporting period.

In GALAXI studies, there were no completed suicide events and no reports of suicidal ideation, suicidal behavior, or self injurious behavior that were serious or resulted in discontinuation of study intervention in patients in the guselkumab and placebo groups that have been reported during the reporting period. Two participants in the guselkumab 200 mg IV→100 mg SC q8w group and one patient in the ustekinumab group reported nonserious event of suicidal ideation without suicidal intent. These events resolved and the participants remained on study intervention. At the screening visit, guselkumab patients had reported a history of depression, anxiety, or suicidal ideation. Another ustekinumab patient reported a nonserious AE of depression leading to discontinuation of study intervention that was considered by the investigator as an event of suicidal ideation. No completed suicide events and no suicidal ideation, suicidal behavior, or self-injurious behavior that were serious or resulted in discontinuation of study intervention occurred in GRAVITI study during the reporting period.

There were 7 cases of ALT or AST ≥5×ULN in guselkumab-treated participants and 1 in an ustekinumab-treated participant. In most cases, the increases in transaminases were nonserious, transient, and resolved while the participants continued to receive guselkumab. No cases met the biochemical criteria of Hy's law. Confounding factors for the guselkumab cases included underlying liver disease, concurrent AEs, or concomitant medications.

As of the most recent assessment cumulatively through 31 March 2024, a total of 127 cases of pregnancy were identified in ongoing and completed interventional clinical studies of guselkumab that have been unblinded. No new safety concerns were identified related to guselkumab exposure during pregnancy.

2.5.1. Discussion on clinical safety

The key safety data to evaluate the safety of guselkumab therapy in patients with moderately to severely active CD are from the GALAXI programme, including 12 weeks IV induction followed by SC maintenance through Week 48, and the GRAVITI study, including 12 weeks SC induction followed by SC maintenance through Week 48. Supportive safety data are provided from the UC studies, and Phase 2 and 3 studies in the approved indications of plaque psoriasis and PsA.

Overall, 1054 participants with CD were exposed to guselkumab with 661 exposed for at least 1 year. The safety database is considered sufficient to characterize the safety profile of guselkumab in the CD indication.

AEs and SAEs frequencies as well as discontinuation due to AE were comparable for all induction doses (1200, 600, 200 mg IV q4w or 400 mg SC q4w) and routes of administration (IV and SC). Slightly, higher overall AEs frequency was observed in the 600 mg iv. induction dose group of GALAXI 1 study. No issue was raised since the lowest induction dose of 200 mg iv was selected for the GALAXI 2 and 3 studies.

Common AEs

Common AEs were led by headache and nasopharyngitis in GALAXI 1 study, both of them occurred with higher frequencies in guselkumab treatment group compared to ustekinumab. In GALAXI 2 and 3 studies, common AEs were led by COVID-19, arthralgia, upper respiratory tract infection, CD, headache, nasopharyngitis and pyrexia. Respiratory tract infections (frequency very common), arthralgia (frequency common) and headache (frequency common) are listed adverse reactions in SmPC section 4.8, hence, no product information update is needed.

Upon the CHMP's request, the MAH reviewed the events of pyrexia. The majority of events of pyrexia were standalone events and not temporally associated with concurrent infections, vaccinations, or CD flares, and most were assessed by the investigator as not related. Pyrexia events were reported at a comparable frequency among the guselkumab and placebo groups. Further, pyrexia can be a symptom of underlying active CD due to the inflammatory process itself. Considering also the lack of a plausible mechanism of development of pyrexia by guselkumab, it is concluded that a causal association between guselkumab and pyrexia cannot be established.

Death and Serious AEs

One death in a guselkumab-treated participant was reported in the CD studies. The death attributed to a gunshot wound was considered not related to study intervention by the investigator. This is agreed by the CHMP.

In GALAXI studies and GRAVITI study, no trends on dose dependence or imbalances between treatment groups were found for SAEs. The majority of gastrointestinal SAEs referred to the CD itself (signs or complications).

In GALAXI 1 study, one case of acute pancreatitis was reported during the maintenance phase. However, this was not considered a concern since severe pancreatitis events is a comorbidity with IBD (Fousekis et al, 2018[16]).

One case of Wernicke's encephalopathy was reported in GALAXI 1 study (the patient experienced also MACE and septic shock). Since Wernicke's encephalopathy is a comorbidity with IBD due to the rapid depletion of thiamine in IBD conditions (Oudman et al, 2021[17]), no concern was raised.

Angina unstable and coronary artery disease occurred in one patient each in the 100 mg sc. maintenance treatment group and in the 200 mg sc. maintenance treatment group of GALAXI 2 study, respectively. Both events occurred in patients with risk factors, no concern was raised.

Targeted AEs

Active TB

[16] Fousekis, Fotios S., et al. "Pancreatic involvement in inflammatory bowel disease: a review." *Journal of clinical medicine research* 10.10 (2018): 743.
[17] Oudman, Erik, et al. "Wernicke's encephalopathy in Crohn's disease and ulcerative colitis." *Nutrition* 86 (2021): 111182.

One case of non-serious extrapulmonary active TB was reported during maintenance (Study Day 99, GALAXI 3 study), in the 200 mg IV → 100 mg SC q8w group in a participant who had tested negative for latent TB at screening from an endemic region. No concerns were raised following review of the case.

Opportunistic infections

Three opportunistic infections reported through the reporting period up to approximately 1 year occurred in the guselkumab treatment groups (1 nonserious case of oesophageal candidiasis and 1 nonserious case of CMV infection in the guselkumab 200 mg IV group during the placebo-controlled induction period of GALAXI 3 and 1 case of active TB in the guselkumab 200 mg IV → 100 mg SC q8w group in GALAXI 3).

Serious infections are important potential risk in the agreed RMP and is monitored through routine and additional pharmacovigilance activities. Further, the risk of infections is sufficiently addressed in SmPC Sections 4.4 and 4.8, hence, no update of the product information is deemed necessary.

Anaphylaxis and Serum Sickness Reactions

There were no reports of anaphylaxis or serum sickness reactions in the guselkumab treatment groups of GALAXI and GRAVITI studies.

MACE

Through the reporting period up to approximately 1 year, MACE (PT: ischemic stroke) was reported in one participant in the guselkumab 200 mg IV → 100 mg SC q8w group with pre-existing cardiovascular risk factors. An additional MACE (PT: myocardial infarction) was reported in a participant who received the guselkumab 600 mg IV → 200 mg SC q4w group of GALAXI 1 during concurrent events of Wernicke's encephalopathy and septic shock. MACE is an important potential risk in the agreed RMP and is monitored through routine and additional pharmacovigilance activities.

VTE

During the placebo-controlled induction period of GALAXI 1 study, 2 VTEs were reported in guselkumab-treated participants who both had risk factors for VTE: one pulmonary embolism in the 1200 mg IV group and one deep venous thrombosis in the 600 mg IV group. The VTE event rates summarized in the CD and UC studies through 1 year of follow-up (0.26 and 0.32 per 100 subject-years, respectively) were consistent with rates of VTE reported in the IBD population (Bernstein 2021[18]; Weng 2018[19]). The CHMP concluded that the data available do not suggest an increased risk of thrombotic events with guselkumab treatment.

Clinically important hepatic disorders

A total of 7 guselkumab-treated participants had clinically important hepatic disorders. One event in the 200 mg IV treatment group met biochemical criteria for Hy's law during the induction period of GALAXI 2 study in a patient diagnosed subsequently with Gilbert's disease. A SAE of DILI was reported in GALAXI 3 study, the event resolved after the treatment discontinuation. There were confounding factors (e.g. concomitant viral infection, treatment of latent TB, treatment with combination of antibiotics) or underlying condition (e.g. Gilbert's disease, fatty liver disease) in all of cases.

[18] Bernstein CN (2021), Nugent Z, Singh H. Persistently high rate of venous thromboembolic disease in inflammatory bowel disease: A population-based study. Am J Gastroenterol. 2021;116(7):1476-1484.

[19] Weng MT (2018), Park SH, Matsuoka K, et al. Incidence and risk factor analysis of thromboembolic events in East Asian patients with inflammatory bowel disease, a multinational collaborative study. Inflamm Bowel Dis. 2018;24(8):1791-1800.

As for clinical chemistry, most of the liver function elevations were between 1 and 3x ULN. Some dose dependence was seen in the induction dose finding study GALAXI 1, as remarkably higher frequencies of various liver enzyme elevations were observed in the 1200 mg iv. induction dose. However, this induction dose was not applied in the Phase 3 CD studies, hence no concern was raised. As for the liver safety of the sc. 400 mg induction dose in GRAVITI study, liver enzyme elevations occurred with comparable or lower frequency in this dose group compared to the iv. induction dose groups in GALAXI studies. For the maintenance phase, no dependency of the liver enzyme elevations by maintenance guselkumab doses was observed. Description of the selected adverse reaction in SmPC Section 4.8 is updated to indicate that based on laboratory assessments in pooled Phase II and Phase III CD clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies.

Haematology results raised no additional concerns on the use of guselkumab in CD. Anaemia is a common and known comorbidity of CD. Neutrophil count decreased is a known ADR of guselkumab (frequency uncommon). Hence, no product information update is needed.

Pregnancy

As of the most recent assessment cumulatively through 31 March 2024, a total of 127 cases of pregnancy were identified in ongoing and completed interventional clinical studies of guselkumab that have been unblinded. No new safety concerns were identified related to guselkumab exposure during pregnancy. Exposure during pregnancy is listed as missing information in the RMP and is monitored through additional pharmacovigilance activities.

Elderly

In clinical trials for the CD indication, there was a higher proportion of participants developing infections in elderly patients (≥ 65 years of age) treated with guselkumab compared to placebo. Results are available for 8/45 guselkumab-treated subjects ≥ 65 years of age experiencing at least 1 event of infection. Further, 6/8 subjects experiencing infection were already on concomitant immunosuppressive treatment for CD. The MAH noted that the number of infections in elderly patients was lower than in patients <65 years of age. Also, elderly patients treated with guselkumab for CD therapy showed fewer infections than patients treated with guselkumab in other indications. In patients <65 years of age, the number of subjects with an event of infection per 100 subject-years was similar between guselkumab and placebo and the underlying data set was more extensive. All of the reported infections resolved, the majority were respiratory tract infections and none was serious. Considering the above, the MAH suggested that there is no increased risk of infection with guselkumab compared to placebo, which is followed by the CHMP. The CHMP noted also the limited data available and agreed that this issue can be monitored via routine phamacovigilance.

The CHMP acknowledged that the safety data available in the elderly are limited. The use in patients ≥ 65 years is listed as missing information in the RMP.

Long-term safety results

Upon the CHMP's request, the MAH provided during the procedure clinical safety data available from the long-term extensions of GALAXI 2, 3 and GRAVITI studies through 15 May 2024. These additional safety data do not suggest a clinically meaningful difference in the safety profile between guselkumab 100 mg SC q8w and 200 mg SC q4w maintenance dose regimens in CD. Long term safety of guselkumab is listed as missing information in the RMP, it is monitored via additional pharmacovigilance activities.

Overall, no new safety concern was identified from the data available in patients with CD. Following updated pooled safety analysis, the frequency of the following adverse reactions are updated in SmPC Section 4.8:

- Hypersensitivity and anaphylaxis: from uncommon to rare
- Injection sites reactions: from common to uncommon

2.5.2. Conclusions on clinical safety

The safety profile of guselkumab in patients with CD is comparable to UC. No new safety concerns are identified in patients with CD. Similar safety profiles are observed for the guselkumab 200 mg iv q4W and guselkumab 400 mg sc q4W induction regimens. The safety profile between guselkumab 100 mg SC q8w and 200 mg SC q4w maintenance dose regimens are comparable in CD.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.2 is acceptable.

Safety concerns

Important identified risks	None
Important potential risks	Serious infection
	Malignancy
	Serum sickness
	Major adverse cardiovascular events (MACE)
Missing information	Exposure during pregnancy
	Use in patients ≥65 years of age
	Long-term safety of guselkumab

Pharmacovigilance plan

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances Not applicable				
Category 3 – Required additional pharmacovigilance activities				
C0168Z03 (PSOLAR) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	20 June 2007: The registry was expanded to include TREMFYA patients on 26 March 2018 and the first TREMFYA patient was enrolled in PSOLAR on 25 February 2019.
			Interim report	4Q 2025
			End of data collection for TREMFYA	4Q 2029
			Final report	4Q 2030
CNTO1959PSO4001 (PsoBest) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	January 2008: The registry was expanded to include TREMFYA patients and the first TREMFYA patient was enrolled in PsoBest in January 2018.
			Interim report	After enrollment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year)
			End of data collection for TREMFYA	To be determined
			Final report	4Q 2030

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Ongoing	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes in infants up to 1 year of age	• Exposure during pregnancy	Protocol submission	August 2018
			Start of data collection	31 December 2022
			Interim report	4Q 2025
			End of data collection	30 June 2030
			Final report	2Q 2031
Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 44 assessments as part of the Maintenance Study. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection	31 July 2020
			End of data collection	3Q 2027
			Final report	3Q 2028
Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 48 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection	
			GALAXI 1	10 May 2018
			GALAXI 2	08 January 2020
			GALAXI 3	22 January 2020
			End of data collection	3Q 2027
			Final reports	3Q 2028

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-term extension of Study CNTO1959UCO3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment following the Week 24 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	2Q 2025
			Start of data collection	13 September 2022
			End of data collection	4Q 2028
			Final report	4Q 2029
Long-term extension of Study CNTO1959CRD3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment following the Week 24 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	January 2025
			Start of data collection	19 January 2022
			End of data collection	2Q 2028
			Final report	2Q 2029

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infection	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029
Malignancy	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serum sickness	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029
Major adverse cardiovascular events (MACE)	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Exposure during pregnancy	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, Pregnancy and Lactation) Package Leaflet Section 2 (What you need to know before you use Tremfya) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up of reported pregnancies **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Final report: 2Q 2031
Use in patients ≥65 years of age	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and Method of Administration) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030
Long-term safety of guselkumab	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tremfya 100 mg solution for injection in pre-filled syringe and Tremfya 100 mg solution for injection in pre-filled pen. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CD is a chronic, progressive, and potentially life-threatening disorder that may affect any part of the GI tract. Symptoms may include diarrhoea, abdominal pain, weight loss/anorexia, and fatigue. Inflammation can cause mucosal ulcerations and can also penetrate the lining of the GI tract, causing intra-abdominal fistulas, in addition to causing painful perianal disease. CD may also be stricturing, such that patients may require repeated surgeries.

The pathophysiology of CD is complex and thought to be multifactorial (D'Haens 2014[20]). The primary aim of pharmacotherapy is to dampen the inflammatory response, thereby relieving symptoms and promoting mucosal healing. The specific goals of CD treatment include control of symptoms, prevention of relapses and complications, restoration and maintenance of quality of life, and absence of disability (Turner 2021[21]).

3.1.2. Available therapies and unmet medical need

The treatment of CD has historically relied on corticosteroids and immunosuppressive medications such as thiopurines or MTX. Corticosteroids are associated with well-known undesired side effects and therefore are not suitable for long-term treatment.

Biologic agents currently approved for the treatment of moderately to severely active CD include: TNF antagonist therapies, an α4β7-integrin inhibitor, an IL-12/23 inhibitor, and an IL-23p19 inhibitor. A Janus kinase (JAK) inhibitor is also approved. Despite the availability of these approved therapies, not all patients respond to induction therapy and many patients who initially respond to the approved therapies may lose response over time. It is estimated that more than half of patients with CD fail to achieve corticosteroid-free clinical remission after 1 year, with even fewer achieving endoscopic

[20] D'Haens GR (2014), Sartor RB, Silverberg MS, Petersson J, Rutgeerts P. Future directions in inflammatory bowel disease management. J Crohn's Colitis. 2014;8(8):726-734.
[21] Turner D (2021), Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.

response or remission (Singh 2021[22]; Vuyyuru 2024[23]). The importance of achieving endoscopic outcomes in CD has been increasingly recognized in recent consensus statements and guidelines to improve long-term outcomes (Christensen 2016[24]; Turner 2021[25]), adding to the unmet need in the treatment of CD. Furthermore, there are associated safety risks with the approved medicines, including warnings related to serious infections, mortality, malignancy, major adverse cardiovascular events, or thrombosis. Hence, there is an unmet medical need for additional efficacious therapeutic options in CD with a favourable safety profile for patients with an inadequate response to or intolerance to conventional or biologic therapies.

3.1.3. Main clinical studies

The efficacy of guselkumab for treating moderately to severely active CD was investigated in 4 studies. Three of the studies evaluated guselkumab IV induction followed by SC maintenance (all 3 studies were conducted under a single protocol, CNTO1959CRD3001, referred to as GALAXI) and the fourth study evaluated guselkumab SC induction followed by SC maintenance (CNTO1959CRD3004; referred to as GRAVITI).

All the studies were conducted with a treat-through design. ie, each participant was randomized to a treatment regimen at Week 0 and remained on that regimen through Week 48 of each study regardless of their clinical response status, with the exception of participants randomized to placebo at Week 0. The GALAXI programme was placebo and active-controlled (ustekinumab). The GRAVITI study was placebo-controlled.

GALAXI 1 study was a Phase 2 dose ranging study, whereas GALAXI 2 and 3 were Phase 3 studies with identical study design. GALAXI 2, 3 and GRAVITI studies were considered as the pivotal studies.

In GALAXI 2, 3 studies, the 4 treatment groups and their corresponding dose regimens from Week 0 through Week 48 are:

- Guselkumab 200 mg IV q4w ×3 induction → 200 mg SC q4w maintenance
- Guselkumab 200 mg IV q4w ×3 induction → 100 mg SC q8w maintenance
- Ustekinumab ~6 mg/kg IV induction → 90 mg SC q8wmaintenance as active control
- Placebo iv. → Placebo or Ustekinumab sc Crossover.

In GRAVITI study, the 3 treatment groups are:

- Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 200 mg SC q4w through Week 24
- Guselkumab 400 mg SC at Weeks 0, 4, and 8, followed by guselkumab 100 mg SC q8w through Week 24
- Placebo SC q4w from Week 0 through Week 24

[22] Singh S (2021), Proctor D, Scott FI, Falck-Ytter Y, Feuerstein JD. AGA Technical Review on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160(7):2512-2556.e9.

[23] Vuyyuru SK (2024), Nguyen TM, Murad MH, et al. Comparative Efficacy of Advanced Therapies for Achieving Endoscopic Outcomes in Crohn's Disease: A Systematic Review and Network Meta-Analysis. Clin Gastroenterol Hepatol. Published online January 6, 2024.

[24] Christensen B (2016), Rubin DT. Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice. Curr Gastroenterol Rep. 2016;18(1):5.

[25] Turner D (2021), Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.

3.2. Favourable effects

In GALAXI 2 study, co-primary efficacy endpoints of Week 12 clinical remission and Week 12 endoscopic response and key secondary endpoints of Week 48 CS-free clinical remission, Week 48 endoscopic response and Week 12 PRO-2 remission were met. The secondary endpoint of Week 12 fatigue response endpoint was met. The composite endpoint of Week 48 clinical remission and endoscopic response and the endpoint Week 48 endoscopic remission vs ustekinumab failed.

In GALAXI 3 study, the co-primary endpoints of Week 12 clinical remission and Week 12 endoscopic response and the key secondary endpoints of Week 12 PRO2 remission and Week 48 CS free remission and endoscopic response were met. The secondary endpoint of Week 12 fatigue response, and the composite endpoint of Week 48 clinical remission and endoscopic response were also met. Endoscopic remission vs ustekinumab was met for the 100 mg sc Q8W guselkumab treatment group but failed in the 200 mg sc. Q4W guselkumab treatment group.

Other Week 48 secondary endpoints showed numeric improvement in the two guselkumab maintenance doses, compared to placebo and similar or higher therapeutic responses compared to ustekinumab in both Phase 3 GALAXI studies.

Improvement in IBDQ total score was observed in guselkumab treatment groups vs placebo at Week 12, the improvements were maintained at Week 48.

In GRAVITI study, the co-primary endpoints of Week 12 clinical remission and Week 12 endoscopic response were met for the guselkumab 400 mg SC treatment group. All secondary endpoints of Week 24 clinical remission for both guselkumab treatment groups, Week 12 PRO-2 remission, and Week 12 clinical response were achieved. The efficacy on clinical remission and endoscopic response was maintained at Week 48.

3.3. Uncertainties and limitations about favourable effects

Long-term clinical efficacy data beyond one-year are limited to Week 152 results in GALAXI 1 Phase 2 study. However, results are available for a limited number of subjects from a single study, hence, no conclusion can be made. The MAH has committed to submit long-term efficacy results up to 5 years of follow-up of the GALAXI 2 and 3 studies post approval (final report expected in Q3 2028).

3.4. Unfavourable effects

The safety profile of guselkumab in patients with CD is similar to the known safety profile of guselkumab. No new safety concerns were identified.

3.5. Uncertainties and limitations about unfavourable effects

Two events of MACE (ischemic stroke, myocardial infarction) were reported in CD patients treated with guselkumab, one event occurred in a patient with pre-existing cardiovascular risk factors the other event was reported concurrently with Wernicke's encephalopathy and septic shock. MACE is already listed as an important potential risk in the RMP and is monitored through routine and additional pharmacovigilance activities including the long-term extension of Study GRAVITI.

There was a higher proportion of participants developing infections in elderly patients (≥ 65 years of age) treated with guselkumab compared to placebo in CD clinical trials. However, only limited data are available, and the increased risk of infections is not confirmed. This issue will be monitored via routine

phamacovigilance. There is limited data on the use in patients ≥ 65 years, this is already listed as missing information in the RMP and is monitored via additional pharmacovigilance activities.

There is limited data on the use of guselkumab in pregnant women. Exposure during pregnancy is already listed as missing information in the RMP and is monitored through additional pharmacovigilance activities.

There is limited data on the long-term use of guselkumab. Long term safety of guselkumab is already listed as missing information in the RMP, it is monitored via additional pharmacovigilance activities including the long-term extension of Study GRAVITI.

3.6. Effects Table

Table 72: Effects Table for guselkumab in the treatment of CD

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
GALAXI 2						
Clinical remission	Week 12	%	200 IV: 47.1	PBO IV: 22.4	<0.025 Co-primary endpoint	GALAXI 2
			200 IV: 47.1	PBO IV: 15.3	<0.025 Co-primary endpoint	GALAXI 3
Endoscopic response	Week 12	%	200 IV: 37.7	PBO IV: 10.5	<0.025 Co-primary endpoint	GALAXI 2
			200 IV: 36.2	PBO IV: 13.9	<0.025 Co-primary endpoint	GALAXI 3
CS free clinical remission	Week 48	%	100 SC: 62.9 200 SC: 71.2	UST SC: 60.8	<0.025 T1 sec EP	GALAXI 2
			100 SC: 64.3 200 SC: 64.0	UST SC: 58.8	<0.025 T1 sec EP	GALAXI 3
Endoscopic response	Week 48	%	100 SC: 49.0 200 SC: 56.2	UST SC: 42.0	<0.025 T1 sec EP	GALAXI 2

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			100 SC: 46.9 200 SC: 49.3	UST SC: 32.4	<0.025 T1 sec EP	GALAXI 3
PRO remission	Week 12	%	200 IV: 42.9	PBO IV: 21.1	<0.025 T1 sec EP	GALAXI 2
			200 IV: 41.6	PBO IV: 13.9	<0.025 T1 sec EP	GALAXI 3
Fatigue response	Week 12	%	200 IV: 45.3	PBO IV: 28.9	<0.025	GALAXI 2
			200 IV: 43.3	PBO IV: 18.1	<0.025	GALAXI 3
Unfavourable Effects						
			GUS combined	PBO		
Overall AEs	By Week 48	%	76.4	69.7	-	GALAXI 2
			77.8	77.8	-	GALAXI 3
Arthralgia	By Week 48	%	9.3	7.9	-	GALAXI 2
			6.8	4.2	-	GALAXI 3
URTI	By Week 48	%	9.0	5.3	-	GALAXI 2
			9.2	9.7	-	GALAXI 3
Crohn's disease	By Week 48	%	8.7	15.8	-	GALAXI 2
			8.9	22.2	-	GALAXI 3
Headache	By Week 48	%	6.2	2.8	-	GALAXI 2
			5.8	5.6	-	GALAXI 3
Nasopharyngitis	By Week 48	%	5.9	3.9	-	GALAXI 2
			5.1	4.2	-	GALAXI 3
Pyrexia	By Week 48	%	5.9	6.6	-	GALAXI 2
			5.8	6.3	-	GALAXI 3

Abbreviations: AE=adverse event, SC=subcutaneous, GUS= guselkumab, IV=intravenous, PBO= placebo, T1 sec EP= Type 1 error control secondary endpoint, URTI= urinary tract infection, UST= ustekinumab

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Clinical efficacy of guselkumab in patients with moderately to severely active CD and with prior failure of conservative or biological therapies was significantly better compared to placebo on a set of co-primary and secondary endpoints which refer to the symptomatic and endoscopic improvement of the baseline condition during the induction and also the maintenance part of the clinical programme. Improvements were also observed on the fatigue response and health-related quality of life IBDQ total score.

Similar or higher therapeutic responses with guselkumab were observed compared to ustekinumab in both Phase 3 GALAXI studies.

Both induction doses of 200 mg iv. and 400 mg sc. at Week 0, 4 and 8 were found effective. Efficacy was shown for 100 mg sc q8w which is the recommended maintenance dose and for 200 mg sc q4w which is recommended for maintenance, alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgment.

The safety profile of guselkumab in patients with CD was in line with the known safety profile of guselkumab.

3.7.2. Balance of benefits and risks

Clinical response and remission observed with guselkumab during both the induction and maintenance phases are clinically relevant in the CD indication. The safety profile of guselkumab in CD is consistent with the known profile of the product.

The benefit risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall benefit/risk of guselkumab is positive in the following indication:

Crohn's disease

Tremfya is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the

following change:

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

Extension of indication to include treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment, based on results from GALAXI Phase 2/3 programme and the GRAVITI Phase 3 study. GALAXI is a Phase 2/3, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter protocol to evaluate the efficacy and safety of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional or biologic therapy. GRAVITI is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of guselkumab SC induction therapy in participants with moderately to severely active CD.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.2 of the RMP is agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMEA/H/C/004271/II/0044.