27 February 2025
EMA/95032/2025 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Tremfya

International non-proprietary name: guselkumab

Procedure No. EMEA/H/C/004271/X/0043/G

## 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

| | |
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| **5-ASA** | 5-aminosalicylic acid |
| **6-MP** | 6-mercaptopurine |
| **ADA** | anti-drug antibodies |
| **ADR** | adverse drug reaction |
| **ADT** | advanced therapy, ie, TNFα antagonists, vedolizumab, or tofacitinib |
| **AE** | adverse event |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **ATC** | Anatomical Therapeutic Chemical |
| **AZA** | azathioprine |
| **CD** | Crohn's disease |
| **CHMP** | Committee for Medicinal Products for Human Use |
| **CI** | confidence interval |
| **CMC** | chemistry, manufacturing, and controls |
| **CMH** | Cochran-Mantel-Haenszel |
| **CMV** | cytomegalovirus |
| **COVID-19** | Coronavirus disease 2019 |
| **CRP** | C-reactive protein |
| **CSR** | Clinical Study Report |
| **C-SSRS** | Columbia-Suicide Severity Rating Scale |
| **eDISH** | evaluation of drug-induced serious hepatotoxicity |
| **ECLIA** | electrochemiluminescent immunoassay |
| **E-R** | exposure-response |
| **EU** | European Union |
| **FDA** | United States Food and Drug Administration |
| **FOIA** | Freedom of Information Act |
| **FVP** | final vialed product |
| **GCP** | Good Clinical Practice |
| **GI** | gastrointestinal |
| **HLT** | high-level term |
| **HRQOL** | health-related quality of life |
| **I** | induction, ie, Week I-12 is induction Week 12 |
| **IA** | interim analysis |
| **IB** | Investigator's Brochure |
| **IBD** | inflammatory bowel disease |
| **IBDQ** | Inflammatory Bowel Disease Questionnaire |
| **ICH** | International Council for Harmonisation |
| **ICE** | intercurrent event |
| **Ig** | immunoglobulin |
| **IL** | interleukin |
| **IRB** | Institutional Review Board |
| **IS-1** | Induction Study 1 (CNTO1959UCO3001 [QUASAR] Phase 2b induction study) |
| **IS-2** | Induction Study 2 (CNTO1959UCO3001 [QUASAR] Phase 3 induction study) |
| **IV** | intravenous |
| **IWRS** | Interactive Web Response System |
| **LLOQ** | lower limit of quantification |
| **LS** | least squares |
| **LTE** | long-term extension |
| **M** | maintenance, ie, Week M-44 is maintenance Week 44 |
| **mAb** | monoclonal antibody |
| **MACE** | major adverse cardiovascular events |

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|---|---|
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MCS** | Mental Component Summary |
| **MTX** | methotrexate |
| **NAb** | neutralizing antibody |
| **NHI** | Nancy Histological Index |
| **NMSC** | nonmelanoma skin cancer |
| **PCS** | Physical Component Summary |
| **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 |
| **PGA** | physician's global assessment |
| **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 |
| **PROMIS-Fatigue SF-5a** | modified PROMIS-Fatigue Short Form 7a consisting of only items 1-5 |
| **PsA** | psoriatic arthritis |
| **PT** | preferred term |
| **q4w** | every 4 weeks |
| **q8w** | every 8 weeks |
| **QUASAR** | CNTO1959UCO3001 (protocol) |
| **RHI** | Robarts Histological Index |
| **RLPH** | real-life patient handling |
| **RMP** | Risk Management Plan |
| **SAE** | serious adverse events |
| **SAP** | Statistical Analysis Plan |
| **SC** | subcutaneous |
| **SCE** | Summary of Clinical Efficacy |
| **SCP** | Summary of Clinical Pharmacology |
| **SCS** | Summary of Clinical Safety |
| **SD** | standard deviation |
| **SI** | International System of Units |
| **SmPC** | Summary of Product Characteristics |
| **SMQ** | Standardized MedDRA Queries |
| **SOC** | system organ class |
| **$t_{1/2}$** | terminal half-life |
| **TB** | tuberculosis |
| **TEAE** | treatment-emergent adverse event |
| **TNF** | tumour necrosis factor |
| **UC** | ulcerative colitis |
| **ULN** | upper limit of normal |
| **US** | United States |
| **VTE** | venous thromboembolism |
| **WPAI-GH** | Work Productivity and Activity Impairment Questionnaire-General Health |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

Janssen-Cilag International N.V. submitted on 29 April 2024 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation:

| Variation(s) requested | | Type |
|---|---|---|
| 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 | II |

Extension application to add a new pharmaceutical form (concentrate for solution for infusion), a new strength (200 mg) and a new route of administration (intravenous use) and to add a new strength of 200 mg for solution for injection (in pre-filled syringe / pre-filled pen) for subcutaneous use in the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor.
This application is grouped with a type II variation (C.I.6a) to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor, as initially claimed, based on results of a Phase 2b/3 clinical development programme (CNTO1959UCO3001) consisting of 3 separate studies, an Induction dose finding Study 1 Phase 2b, an Induction Study 2 Phase 3 and a Phase 3 Maintenance Study. These studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of guselkumab in participants with moderately to severely active UC. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC of the already approved form 100 mg solution for injection are updated. The Package Leaflet and Labelling are updated in accordance. Version 10.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes to the PI.

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

## *1.3. Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0190/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0190/2023 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. 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.

## *1.5. Scientific advice*

The MAH received Scientific advice from the CHMP on 28 March 2019 (EMEA/H/SA/3614/2/2019/II). The Scientific advice pertained to clinical aspects.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Beata Maria Jakline Ullrich

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| The application was received by the EMA on | 29 April 2024 |
| The procedure started on | 23 May 2024 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 16 August 2024 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 20 August 2024 |
| The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on | 28 August 2024 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 05 September 2024 |
| The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on | 19 September 2024 |
| The MAH submitted the responses to the CHMP consolidated List of Questions on | 11 October 2024 |
| The CHMP and PRAC Rapporteurs circulated the CHMP and PRAC Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 22 November 2024 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 28 November 2024 |
| The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 06 December 2024 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on | 12 December 2024 |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 28 January 2025 |
| The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 31 January 2025 |

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| The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 12 February 2025 |
| The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 20 February 2025 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tremfya on | 27 February 2025 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Ulcerative colitis (UC) is an inflammatory bowel disorder of unknown aetiology characterized by chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors (Ordás 2012[a]; Danese 2004[b]; Podolsky 2002[c]; Stenson 2000[d]). UC is characterized by a life-long relapsing and remitting course, with 15% of patients having an acute exacerbation requiring hospitalization at some time during their illness (Willert 2008[e]). In severe UC, the bowel wall may become extremely thin, the mucosa denuded, and the inflammation may extend to the serosa leading to dilatation, toxic megacolon, and subsequent perforation (Glickman 1998[f]; Stenson 2000[g]). Within 10 years of diagnosis, approximately 20% of adults with UC are reported to have undergone colectomy (Van Limbergen 2008[h]).

### 2.1.2. Epidemiology

The prevalence rates for UC are between 2.4 to 505 per 100,000 persons in Europe (Ng et al. 2017[i]).

[a] Ordás I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619.
[b] Danese S (2019), Allez M, van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Dig Dis. 2019;37(4):266-283.
[c] Podolsky DK (2002). Inflammatory bowel disease. N Engl J Med. 2002;347(6):417-429.
[d] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[e] Willert RP (2008), Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependant and refractory ulcerative colitis. World J Gastroenterol. 2008;14(16):2544-2549.
[f] Glickman RM (1998). Inflammatory bowel disease: ulcerative colitis and Crohn's disease. In: Faluce AS, Braunwald E, eds. Harrison's Principles of Internal Medicine, 14th ed. New York, NY: McGraw-Hill;1998;1633 1645.
[g] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[h] Van Limbergen J (2008), Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135(4):1114-1122.
[i] Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., ... & Kaplan, G. G. (2017). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet*, *390*(10114), 2769-2778.

Ulcerative colitis is a serious disease. The onset of ulcerative colitis is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates.

### 2.1.3. Aetiology and pathogenesis

The precise aetiology of UC is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora in a genetically susceptible host, finally leading to chronic intestinal inflammation.

### 2.1.4. Clinical presentation, diagnosis

Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, bowel urgency, fatigue, fever, and may also display prominent extraintestinal manifestations, most commonly arthritis (Regueiro 2023[a]; Ordás 2012[b]; Stenson 2000[c]; Caron 2023[d]; Dubinsky 2022[e]).

### 2.1.5. Management

Conventional therapies for the treatment of UC include 5-ASA–containing medications, corticosteroids, and immunomodulators such as azathioprine (AZA) and 6-mercaptopurine (6-MP) (Kobayashi 2020[f]). Treatment with 5-ASA therapy has been shown to be efficacious and safe as monotherapy for induction of moderately but not severely active UC. Corticosteroids are effective for the induction of remission but are not an option for maintenance therapy due to cumulative toxicity and lack of long-term efficacy. Thiopurines are slow acting and monotherapy with thiopurines does not induce remission in moderately to severely active UC. Treatment with biologics or small molecules may be considered if corticosteroids or immunomodulators fail to achieve or maintain remission (Revés 2021[g]; Côté Daigneault 2015[h]). However, clinical guidance supports early use of biologics rather than gradual step-up therapy in patients with moderate to severe disease activity at increased risk for colectomy (Feuerstein 2020[i]). Delaying effective treatment to induce remission may be harmful and increase the risk of UC-related complications, hospitalisation, colectomy, and inferior quality of life in patients with predictors of colectomy such as extensive UC disease, severe endoscopic activity, early need for corticosteroids, and elevated inflammatory markers (Yarur 2011[j]; Burisch 2017[k]).

[a] Regueiro M (2023), Hunter T, Lukanova R, et al. Burden of fatigue among patients with ulcerative colitis and Crohn's disease: results from a global survey of patients and gastroenterologists. Adv Ther. 2023;40(2):474-488.
[b] Ordás I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619.
[c] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[d] Caron B (2023), Ghosh S, Danese S, Peyrin-Biroulet L. Identifying, Understanding, and Managing Fecal Urgency in Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2023;21(6):1403-1413.
[e] Dubinsky MC (2022), Panaccione R, Lewis JD, et al. Impact of Bowel Urgency on Quality of Life and Clinical Outcomes in Patients With Ulcerative Colitis. Crohns Colitis 360. 2022;4(3):otac016.
[f] Kobayashi T (2020), Siegmund B, Le Berre C, et al. Ulcerative colitis. Nat Rev Dis Primers. 2020;6(1):74.
[g] Revés J (2021), Ungaro RC, Torres J. Unmet needs in inflammatory bowel disease. Curr Res Pharmacol Drug Discov. 2021;2:100070.
[h] Côté-Daigneault J (2015), Bouin M, Lahaie R, Colombel J-F, Poitras P. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterology Journal. 2015;3(5):419-428.
[i] Feuerstein JD (2020), Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020;158(5):1450-1461.
[j] Yarur AJ (2011), Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2011;7(10):652-659.
[k] Burisch J (2017), Ungaro R, Vind I, et al. Proximal disease extension in patients with limited ulcerative colitis: a danish population-based inception cohort. Journal of Crohn's and Colitis. 2017;11(10):1200-1204.

Approved biologic therapies for the treatment of UC include anti-TNFα agents, an α4β7 integrin antagonist, an anti-IL-12/23 antibody and an anti-IL-23 antibody mirikizumab. Small molecule advanced therapies include JAK inhibitors and S1P receptor modulators. Approximately one third of patients do not respond initially to advanced therapies, and an additional 10% of responders lose their initial response over the course of treatment, resulting in treatment switch or dose adjustment (Afzali 2023[a]; Privitera 2021[b]; Danese 2019[c]; Sands 2019[d]). Furthermore, there are associated safety risks with some currently approved advanced therapies, including warnings related to serious infections, mortality, malignancy, major adverse cardiovascular events, or thrombosis.

Surgery may be pursued in severe refractory UC. Surgery involves complete removal of potential disease-bearing tissue and may require removing the entire colon and rectum. Surgery is associated with reduced quality of life and risk of complications including pouchitis, stricture, pelvic sepsis, faecal incontinence, sexual dysfunction, and female infertility (Matsuoka 2023[e]; Guaraldi 2018[f]; Ramos-Andrade 2016[g]; Hahnloser 2007[h]).

In summary, there is an unmet medical need for additional efficacious therapeutic options with novel mechanisms of action in UC and a favourable safety profile for patients with an inadequate response to or intolerance to conventional and/or advanced therapies, especially over the long term.

## *2.2. About the product*

Guselkumab is a fully human IgG1, λ antibody , with a wild-type Fc domain, that binds the IL-23p19 subunit of IL-23 and blocks IL-23 signaling. CD64 (Fc-gamma receptor 1) is a cell surface receptor that binds the Fc domain of IgG antibodies; it is the only FcγR with high affinity for IgG1 (Bruhns 2009[i], Bruhns 2015[j]). Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, CD and UC (Mehta 2021[k], Chapuy 2019[l], Chapuy 2020[m]). Guselkumab has demonstrated in vitro blocking of IL-23 signaling and binding to CD64. Taken together, these results indicate guselkumab has the potential to neutralize IL-23 at its cellular source in inflamed tissues.

[a] Afzali A (2023), Lukanova R, Hennessy F, et al. Unmet Needs in Real-World Advanced Therapy-Naïve and -Experienced Patients with Moderately to Severely Active Ulcerative Colitis in the United States. Adv Ther. 2023;40(4321–4338).
[b] Privitera G (2021), Pugliese D, Rapaccini GL, Gasbarrini A, Armuzzi A, Guidi L. Predictors and Early Markers of Response to Biological Therapies in Inflammatory Bowel Diseases. J Clin Med. 2021;10(4):853.
[c] Danese S (2019), Allez M, van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Dig Dis. 2019;37(4):266-283.
[d] Sands BE (2019), Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-1214.
[e] Matsuoka K (2023), Yamazaki H, Nagahori M, et al. Association of ulcerative colitis symptom severity and proctocolectomy with multidimensional patient-reported outcomes: a cross-sectional study. J Gastroenterol. 2023;58(8):751-765.
[f] Guaraldi G (2018), Malagoli A, Calcagno A, et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65 - 74 years and more than 75 years. BMC Geriatr. 2018;18(1):99.
[g] Ramos-Andrade D (2016), Andrade L, Ruivo C, Portilha MA, Caseiro-Alves F, Curvo-Semedo L. Imaging the postoperative patient: long-term complications of gastrointestinal surgery. Insights Imaging. 2016;7(1):7-20.
[h] Hahnloser D (2007), Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg. 2007;94(3):333-340.
[i] Bruhns, P., Iannascoli, B., England, P., Mancardi, D. A., Fernandez, N., Jorieux, S., & Daëron, M. (2009). Specificity and affinity of human Fcγ receptors and their polymorphic variants for human IgG subclasses. *Blood, The Journal of the American Society of Hematology*, *113*(16), 3716-3725.
[j] Bruhns, P., & Jönsson, F. (2015). Mouse and human FcR effector functions. *Immunological reviews*, *268*(1), 25-51.
[k] Mehta, H., Mashiko, S., Angsana, J., Rubio, M., Hsieh, Y. C. M., Maari, C., ... & Sarfati, M. (2021). Differential changes in inflammatory mononuclear phagocyte and T-cell profiles within psoriatic skin during treatment with guselkumab vs. secukinumab. *Journal of Investigative Dermatology*, *141*(7), 1707-1718.
[l] Chapuy L (2019), Bsat M, Sarkizova S, et al. Two distinct colonic CD14+ subsets characterized by single-cell RNA profiling in Crohn's disease [published correction appears in Mucosal Immunol. 2020 Mar;13(2):381]. Mucosal Immunol. 2019;12(3):703-719.
[m] Chapuy L (2020), Bsat M, Rubio M, et al. IL-12 and Mucosal CD14+ Monocyte-Like Cells Induce IL-8 in Colonic Memory CD4+ T Cells of Patients With Ulcerative Colitis but not Crohn's Disease. J Crohns Colitis. 2020;14(1):79 95.

Guselkumab is approved for the treatment of adults with moderate to severe plaque psoriasis and/or adults with active psoriatic arthritis at a dosing regimen of 100 mg SC at Weeks 0 and 4, followed by a maintenance dose every 8 weeks (q8w). In PsA, 100 mg SC q4w dosing regimen may be considered for patients at high risk for joint damage according to clinical judgment.

In this application, the following indication was initially applied:

*TREMFYA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor.*

The posology, as initially applied, was:

*The proposed induction dose is 200 mg by intravenous infusion at Week 0, Week 4, and Week 8.*

*The proposed maintenance dose is 100 mg administered by subcutaneous injection at Week 16 and every 8 weeks thereafter after completion of induction dosing.*

*A dose of 200 mg administered by subcutaneous injection at Week 12 and every 4 weeks thereafter may be considered for patients who do not show adequate therapeutic benefit, according to clinical judgement, after completion of induction dosing.*

*Immunomodulators and/or corticosteroids may be continued during treatment with guselkumab. In patients who have responded to treatment with guselkumab, corticosteroids may be reduced or discontinued in accordance with standard of care.*

*Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.*

## *2.3. Type of Application and aspects on development*

The clinical development programme for guselkumab in UC was designed to evaluate the efficacy and safety of guselkumab in the treatment of adults with moderately to severely active UC who had an inadequate response, loss of response, or intolerance to conventional therapies and/or advanced therapies (ie, TNFα antagonists, vedolizumab, or tofacitinib).

The development programme consisted of 2 controlled Phase 3 studies: an IV Induction Study 2 (hereafter referred to as IS 2) and a randomized withdrawal SC Maintenance Study. These studies were supported by a Phase 2b IV induction dose-ranging study (Induction Study 1; hereafter referred to as IS-1). All 3 studies were conducted under a single protocol, CNTO1959UCO3001 (QUASAR). Together these studies provide at least 1 year (≥56 weeks; at least 12 weeks of IV induction and 44 weeks of SC maintenance) of guselkumab treatment experience.

Participants who completed the safety and efficacy evaluations at Week M-44 of the Maintenance Study and may benefit from continued study intervention had the opportunity to participate in the LTE. The LTE will provide an additional 4 years of treatment to evaluate the efficacy and safety of long term maintenance treatment.

## *2.4. Quality aspects*

### 2.4.1. Introduction

This is an extension application to add a new pharmaceutical form (Concentrate for solution for infusion), a new concentration (10 mg/mL), a new route of administration (intravenous, IV) and a new strength (200 mg). The extension application is grouped with a type II variation (C.I.6.a) for an extension of indication to include the treatment of ulcerative colitis (UC) in adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment.

Tremfya is currently authorised for subcutaneous use in presentations containing 100 mg gusekumab (100 mg/ml) in a pre-filled syringe or pre-filled pen and indicated for the treatment of plaque psoriasis and psoriatic arthritis in adults.

The following new finished product (FP) presentations are introduced with this application:

- A vial containing 200 mg/20 mL (10 mg/mL) guselkumab as concentrate for solution for intravenous infusion. This is referred to as final vialed product (FVP).
- A prefilled syringe (PFS) containing 200 mg/2 mL (100 mg/ml) guselkumab as solution for subcutaneous injection. This is referred to as PFS-U. The PFS-U is available in pack sizes of one or two pre-filled syringes.
- A prefilled pen (PushPen) containing 200 mg/2 mL (100 mg/ml) guselkumab as solution for subcutaneous injection. This is referred to as PFS-Y. The PFS-Y is available in pack sizes of one or two pre-filled pens.

Other ingredients for the 10 mg/mL FVP are: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80, methionine, EDTA disodium dihydrate and water for injections. The primary packaging of the FVP consists of a 25R type I clear glass vial closed with a butyl rubber stopper, an aluminium seal and polypropylene flip top.

Other ingredients for the PFS-U and PFS-Y presentations are: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80 and water for injections. The primary packaging of the PFS-U is composed of a 2.25-mL glass syringe with a bromobutyl rubber stopper with a fixed needle and a needle shield, assembled in an automatic needle guard. The PFS-U is further assembled into PFS-Y with a delivery device.

The 10 mg/mL FVP has a new formulation, adjusted to the new pharmaceutical form, concentrate for solution for infusion. The formulation of the 200 mg PFS-U/PFS-Y presentations is identical to the already approved 100 mg solution for injection, except for the new fill volume of 2 mL.

### 2.4.2. Active substance

Guselkumab is a fully human IgG1λ monoclonal antibody against IL-23. It neutralises the biological activities of the cytokine. The guselkumab active substance (AS) is manufactured by Biogen, Inc., Research Triangle Park, in North Carolina, USA, and Janssen Biologics (Ireland) in Cork, Ireland.

There is no change to the active substance section. The approved guselkumab formulated active substance for the 100 mg FVP and PFS FP presentations is also used for manufacturing of the new proposed 200 mg presentations (FVP and PFS FP).

## 2.4.3. Finished medicinal product

### *2.4.3.1. Description of the product and Pharmaceutical development*

Two pharmaceutical forms are proposed for the finished product: Final vialed product (FVP) as concentrate for solution for infusion containing 200 mg/20 mL (10 mg/mL) guselkumab as active substance, and a sterile solution for injection in a single use, prefilled syringe (PFS-U) or in a prefilled pen combined with a PushPen device for injection (PFS-Y), containing 200 mg/2 mL guselkumab as active substance.

Other ingredients for the 10 mg/mL FVP are: sucrose, Histidine, Polysorbate 80, L-Methionine, EDTA disodium dihydrate. The primary packaging of the FVP consists of a 25R type I clear glass vial closed with a butyl rubber stopper, an aluminium seal and polypropylene flip top.

Other ingredients for the PFS-U and PFS-Y presentations are: Sucrose, Histidine, Polysorbate 80. The primary packaging of the PFS-U is composed of a 2.25-mL glass syringe with a bromobutyl rubber stopper with a fixed needle and a needle shield, assembled in an automatic needle guard. The PFS-U is further assembled into PFS-Y with a delivery device.

Further details on the product formulations are reflected in Table 1 and Table 2.

The 10 mg/mL FVP is supplied as a sterile liquid. Each vial contains 200 mg of guselkumab in a 20 mL nominal fill volume, and an overfill of 0.9 mL per vial is applied.

**Table 1: Composition of FVP (200 mg/20 mL concentrate for solution for infusion)**

| Ingredient | Reference | Function |
|---|---|---|
| Guselkumab | Company standard | Active |
| L-Histidine | Ph. Eur. | Buffer |
| L-Histidine Monohydrochloride Monohydrate | Ph. Eur. | Buffer |
| Sucrose | Ph. Eur. | Stabilizer |
| Polysorbate 80 | Ph. Eur. | Surfactant |
| L_Methionine | Ph. Eur. | Antioxidant |
| EDTA disodium dihydrate | Ph. Eur. | Stabilizer/Chelator |
| Water for Injections | Ph. Eur. | Solvent |

The 200 mg/mL PFS is supplied as a sterile liquid. Except for the fill volume, the formulation for the 200 mg solution for injection is the same as for the approved 100 mg solution for injection. Each prefilled syringe contains 200 mg of guselkumab in 2mL. An overfill of 0.07 mL is applied to deliver the nominal fill volume.

**Table 2: Composition of PFS-U/PFS-Y (200 mg/2 mL solution for injection)**

| Ingredient | Reference | Function |
|---|---|---|
| Guselkumab | Company standard | Active |
| Sucrose | Ph. Eur. | Stabilizer/Tonificier |
| L-Histidine | Ph. Eur. | Buffer |
| L-Histidine Monohydrochloride Monohydrate | Ph. Eur. | Buffer |
| Polysorbate 80 | Ph. Eur. | Surfactant |
| Water for Injections | Ph. Eur. | Solvent |

The primary packaging of the PFS-U FP is composed of a 2.25-mL syringe with a staked 27G half-inch stainless steel needle, covered with a needle shield, stoppered with an elastomer plunger stopper. PFS-U FP is further assembled into PFS-Y FP with a delivery device. Notified Body opinions on the prefilled syringe and the PushPen devices of PFS FP (PFS-Y) were submitted with this application. The use of the name, PushPen for the autoinjector device for the 200 mg PFS has been justified.

No novel excipients or excipients of human or animal origin are used in the formulations. All excipients are of Ph.Eur. quality.

The description and composition of both FVP and PFS finished products is overall adequately described.

Pharmaceutical development

The applicant submitted information on formulation development for the proposed new finished products.

FVP

The diluted FP solution is sterile-filtered and filled into 25R Type I glass vials at a target fill volume of 20.9 mL/vial (0.9 mL overfill) to produce the 200 mg/vial FVP FP.

The 10 mg/mL FP formulation was developed based on supporting data from previous formulation studies conducted during development and commercialisation of the Tremfya 100 mg PFS FP. pH, buffer type, stabilizers, and surfactants were evaluated. Additional development studies were conducted to justify the PS80 concentration and the selection and concentrations of the stabilisers, EDTA disodium dihydrate and L-methionine, added for the 10 mg/mL FP to minimise protein oxidation. Formulation robustness- and photostability studies were also conducted. The rationale for excipients selection in FVP formulation is explained below, with acceptable use of antioxidants and surfactants:

- L-histidine provides buffering capacity at pH 5.8, reduces fragment and aggregate formation. Buffer selection and pH were leveraged from the commercial 100 mg PFS development.
- Sucrose supports the stability profile for the FP, and it is compatible with IV administration. The selection of sucrose as tonicifier, relied upon the previous development experience.
- Polysorbate 80 protects the FP from physical (freeze/thaw or agitation) stress-induced instability. PS80 level (0.05% (w/v)) in the formulation for the 10 mg/mL FP was selected based on the previous formulation development experience for the commercial 100 mg PFS.
- L-Methionine and EDTA disodium dihydrate are added to prevent guselkumab oxidation at low protein concentrations and degradation by oxidation during storage.

According to the target product profile, the 10 mg/mL guselkumab finished product (FVP FP) was developed as a sterile liquid dosage form with at least 24 months shelf life at 2-8 °C. The development strategy for the FVP formulation was leveraged from the previous development experience with the 100 mg/mL PFS and in parallel with the clinical development program. The manufacturing process is adequately characterised and validated. The control strategy is based on the development studies, development production campaigns, clinical production campaigns, and process validation. The composition of guselkumab FP has not been modified or revised during clinical development, and the formulation intended for commercial supply is the same as that of the non-clinical and clinical batches.

Sufficient information is provided on the commercial manufacturing process development of the FVP FP, producing Phase 3 and process validation batches using the same equipment at the same facility that will be used for commercial production. Targets and ranges for process parameters and acceptance criteria for in-process control (IPC) tests were established based on lab-scale process studies. Thawing of AS, compounding of FP solution, sterile filtration, aseptic filling, stoppering, and capping were evaluated. Hold time studies were performed to evaluate in-process hold steps and cumulative exposure to ambient light. The ranges for in process controls (IPCs) are acceptable. CQAs are defined by the Applicant.

PFS

200 mg guselkumab FP is developed as a sterile liquid dosage form with at least 24 months shelf life at 2-8 °C in a prefilled syringe (PFS) for subcutaneous (SC) administration, to deliver 200 mg (100 mg/mL, 2 mL) of guselkumab. The 200 mg FP uses the same active substance as the currently approved 100 mg PFS (100 mg/mL). During FP manufacture, the AS is aseptically filled directly into the syringe barrels, as the target FP solution concentration and formulation are the same as the AS.

A justification of the formulation composition selected for the FP has been provided. However, development studies that support the selected final formulation are not repeated, as the formulation is identical with the formulation of the authorised 100 mg PFS. This is considered acceptable.

The manufacturing process is adequately characterised and validated. The control strategy is based on the development studies, development production campaigns, clinical production campaigns, and process validation. Process validation for the commercial process for manufacture of the 200 mg PFS at larger scale is described. At smaller scale the commercial process validation was leveraged from the authorised 100 mg PFS formulation. The process control strategy development was described, with identification of additional CQAs for the 200 mg FP. Process control strategy development and the history of analytical methods development is overall adequately described.

Container closure development is overall well described for both FPs formulations. Long-term leachable studies at shelf-life conditions were completed. Results (24-month) were provided and are considered acceptable.

For FVP FP the primary container closure system development, microbiological attributes and the in-use compatibility of the 10 mg/mL FP with 0.9% sodium chloride IV solution, and with the direct contact materials during dose preparation and administration were presented. For PFS FP, the primary container closure system development is detailed. Operation, components and assembly of PFS-Y FP, manufacturers and suppliers, control strategy and relevant standards are described.

### *2.4.3.2. Manufacture of the product and process controls*

The batch release site of FVP FP and PFS FP is Janssen Biologics, The Netherlands.

Adequate information has been provided to confirm compliance with GMP.

The FVP FP is manufactured using frozen 100 mg/mL AS. The manufacturing process of FVP FP is standard and consists of the following steps: thawing of AS (and optional storage step, if needed), compounding (and optional storage step, if needed) of dilution buffer, compounding of FP solution (pooling of AS by pre-filtration followed by dilution buffer pre-filtration and dilution/mixing of FP solution), sterile filtration, aseptic filling, and stoppering of FP vials, capping, visual inspection, and

additional post-fill process steps (labelling, secondary packaging, cold storage). Each step is discussed in sufficient detail.

The PFS FP is manufactured using frozen 100 mg/mL AS. The AS is thawed, pooled, mixed, and pre-filtered. The resulted FP solution is sterile filtered and aseptically filled into 2.25 mL syringes and stoppered to achieve nominal 200 mg PFS. The PFS are then visually inspected, stored at 2-8 °C, and assembled into a delivery device system. IPCs are monitored during manufacturing.

PFS-U FP
Assembly of the 200 mg PFS FP with the 2 ml UltraSafe Plus PFS at Cilag is a fully automated process. All 2 mL UltraSafe Plus device components are the PFS, plunger rod, finger flange, and needle guard subassembly. Monitoring of the alignment and positioning of the device subassembly/components and PFS is also automated.

PFS-Y FP
Assembly of 200 mg PFS FP with the YpsoMate PFP at Cilag is a fully automated process. During assembly, proper alignment, and positioning of the device subassembly/components and PFS are ensured by using dedicated format parts and fixtures. The assembly step is controlled via distance (position) and assembly force control.

Hold times at each process steps were justified. Critical and non-critical process parameters (CPPs and nCPPs) in the FVP FP manufacturing process with their operating targets and proven acceptable ranges (PARs) are set. IPC tests and the associated acceptance criteria are provided.

The batch size is defined by the volume of AS available. Batch formula for both FPs is provided.

The control strategy is well designed, and IPCs are adequate to control the FPs consistent quality. Acceptance ranges are overall acceptable.

Process validaton /verification

The manufacturing process for the FVP was validated using three consecutive compounding AS batches that were filled into three consecutive FP batches at the commercial manufacturing site. The manufacturing process for the PFS was validated using three consecutive compounding validation batches that were filled into four consecutive FP filling batches at the commercial manufacturing site. For both FVP and PFS the process was validated to allow pooling of multiple AS batches to create one compounding batch during the manufacture of FP.

Process validation for the PFS-U and PFS-Y assembly was executed on the commercial assembly line using the commercial assembly process and process controls. All equipment used for validation studies were qualified prior to process validation and were operated within qualified ranges during the process validation. For both PFS-U and PFS-Y, validation consisted of 3 representative commercial-scale validation runs.

Full process validation was performed for each step of the FP manufacturing process for both FVP and PFS presentations. Hold times, analytical procedures and shipping methods were validated. For PFS-U and PFS-Y, manufacture and transfer methods were validated. The validation campaign was overall well designed.

### *2.4.3.3. Product specification*

The specifications cover the aspects required as identity, purity, potency, and quantity. The selection of CQAs for release and stability testing is approvable. For the subcutaneous presentation, the usability aspects are also covered adequately. Upon request, identifiers for the in-house analytical methods of both presentations of the FP have been added to the tabular presentations of the specifications.

A detailed explanation of establishing the release and shelf life specification limits has been provided for the FVP and the PFS presentations separately. The proposed acceptance criteria are considered mostly well founded.

For the FVP presentation, the total manufacturing experience was taken in account for calculating specification limits. Clinical subset of the batch data was not considered as the FVP batches were not used in the pivotal clinical trials. However, clinical experience with the 100 mg and the 200 mg PFS presentations was considered. This approach is supported by the identity of the AS, comparability studies and a clinical study that has demonstrated the bioequivalence between the FVP and the 100 mg PFS presentation. It may be questioned, however, whether clinical experience gained by subcutaneous administration can be applied on a product for intravenous infusion in every aspect. In response, the Applicant referred to experience gained through a clinical trial supporting the safety of the proposed criterion. The applicant committed to adjust specifications as appropriate once the release test results of 30 batches will be available (Recommendation 1).

Concerning the PFS presentation, the actual release and stability ranges have been calculated from the clinical subset of batch data (FP batches used in pivotal clinical studies). The ranges have also been calculated on the basis of total manufacturing experience pointing to the representativeness of the clinical data subset for the commercial batches. The functionality test acceptance criteria for the 200 mg PFS presentation assembled with the UltraSafe Plus passive needle guard (PFS-U) as well as for the 200 mg PFS assembled with the YpsoMate device (PFS-Y) are considered justified.

The risk of any nitrosamine impurity is considered low. A detailed risk assessment for the FVP presentation has been provided. For the 200 mg presentation, the nitrosamine risk assessment for the 100 mg presentation was applied. This is considered acceptable.

A safety assessment on the potential elemental impurities is presented, without identified risks for the presence of elemental impurity exceeding the permitted level.

Analytical procedures

The analytical procedures largely correspond to those approved for the 100 mg PFS presentation, certain tests are adapted for the 10 mg/ml FVP presentation, as appropriate. Method descriptions are clear and adequately detailed.

Detailed validation reports have been provided for the analytical methods used for release and stability tests of the FVP presentation. Concerning the 200 mg/2 ml PFS presentation, the validation data on the approved 100 mg PFS analytical procedures has been leveraged as the same active substance is used to manufacture the 200 mg PFS and the composition of the FP is the same. Additional verification and validation studies were performed for tests impacted by fill volume and container closure. This approach is considered acceptable.

The non-compendial analytical procedures are considered validated. For compendial procedures endotoxin and sterility, verification reports from the testing laboratories have been provided.

Reference standards

There is no change to approved reference standards, which remain applicable for the new presentations.

Batch analyses

For the FVP, batch analysis data has been provided for development, clinical and process validation batches.

For the 200 mg PFS, batch analysis data has been provided for development, clinical and process validation batches.

The results confirm consistency of the manufacturing process.

Container closure system

Adequate and detailed descriptions have been provided for the container closure system components for all intended new presentations, including confirmation of compliance of components with ISO requirements, Ph. Eur., technical drawings and dimensions.

For the FVP presentation, 25R Type I glass European Blow Back (EBB) vials (Schott AG) are used. Dry heat sterilisation of the vials is performed at the manufacturing site. Rubber stoppers are received either ready-to-sterilize or ready-to-use. Regarding the PFS, the syringe barrel with staked needle and rigid needle shield, and the plunger stopper are sterilised by ethylene oxide, and are sterilized by the supplier. The plunger rod, finger flange, and needle guard subassemblies of the PFS-U presentation do not come into contact with the product. Neither do the syringe unit and the drive unit of the YpsoMate autoinjector. These subassemblies are not sterile.

Syringe barrel and the plunger stopper components of the PFS are pre-siliconized by the manufacturer with medical grade silicone oil, compliant with the Ph. Eur. 3.1.8 monograph. Silicone oil content of the barrel was tested on development, clinical, and process validation batches, and it was demonstrated that overall, it is at least 5 times lower than the permitted daily exposure (100 µg/day).

Each incoming lot of the primary packaging materials is inspected and tested before release to the manufacturing. After the initial visual inspection, additional visual and physical inspections are performed. For the vials, the testing is based on compendial testing for glass, reference is made to the relevant USP, Ph. Eur. and JP. The physical inspections include functionality tests for the PFS, PFS-U and PFS-Y device components. Each incoming empty syringe barrel lot is tested for piston travel force using the specified plunger stopper. Specifications regarding the functionality tests of the UltraSafe device components: needle guard, plunger rod and the finger fledge are provided, as well as specifications regarding the functionality tests of the YpsoMate autoinjector.

A brief description of secondary packaging is included. It protects the finished product from light exposure.

### *2.4.3.4. Stability of the product*

A shelf life of 24 months stored at 5 ± 3°C and protected from light is proposed for the new presentations.

Stability studies were performed in accordance with ICH guidelines Q1A, Q1B, Q5C and Q5E. Stability studies were conducted under long-term storage conditions (5 ± 3°C), and supportive data were collected under accelerated (25 ± 2°C/60 ± 5% RH) and under stress temperature conditions (40 ± 2°C/75 ± 5% RH). The PFS presentations were subjected to device functionality stability studies.

Storage of the vial presentation (for stability studies include 1 development batch (IIS1H/IIS3L) placed in the upright orientation while all other batches are placed in the inverted orientation to maximise contact of the product to the container closure surfaces. Storage of PFS products is in horizontal position. All containers used in the stability studies are the same as those proposed for routine commercial storage.

Stability results for all presentations and all batches stored at 2-8°C were within the proposed shelf life specifications up to 24 months, or further where tested. The Applicant commits to complete stability testing up to 36 months.

Methods used for stability testing are the same as those described for release. Regarding the FVP stability, the testing panel includes all tests presented in the release specification panel except for some tests where the omission from the stability testing panel is justified and deemed acceptable.

Regarding the PFS presentation, the stability testing panel includes all tests presented in the release specification panel except for some test where the omission from the stability testing panel is justified as the Applicant demonstrated that these attributes do not change over time.

Functionality testing of the PFS-U presentation included needle shield removal force, needle guard activation force, needle guard defeat force and delivered volume. Functionality testing of the PFS-Y included cap removal force, actuation force, needle protrusion length, delivered volume, cover sleeve defeat force and injection time.

For the FVP, adequate data has been provided to support the in-use storage time of up to 10 hours at to 25°C for the diluted infusion solution.

Photostability studies have been performed on the FVP and PFS presentations. The photostability study was conducted in different levels of packaging: in vial, market pack and market pack with aluminium foil. The results demonstrate that the FP, when protected by the representative package and exposed to light conditions (a minimum of 126 hours of combined cool white and UV exposure), at 25 °C, remains essentially unchanged and in conformance with the proposed commercial stability acceptance criteria.

Based on the data provided, the proposed shelf life of 24 months at 5 ± 3 °C, protected from light, is deemed acceptable.

#### *2.4.3.5. Adventitious agents*

There is no change to approved adventitious agent's safety evaluation, which remains applicable.

## 2.4.4. Discussion on chemical, and pharmaceutical aspects

This application is presented as a grouping of a line extension and type II (C.I.6.a scope) variation. The line extension includes the addition of a new pharmaceutical form (Concentrate for solution for infusion), a new concentration (10 mg/mL) a new route of administration (IV) and a new strength (200 mg). The new presentations are aimed for the treatment of ulcerative colitis (UC) in adults.

The same active substance as for the approved Tremfya 100 mg solution of injection is used. Therefore, only the FP dossier is submitted for the marketing approval of the two different FP presentations:

- A 20 ml, 200 mg vial, concentrate for solution for infusion
- A 2 ml, 200 mg prefilled syringe product which differs from the approved 100 mg PFS product only in the size of the presentation (the formulation is the same) and in the container closure system. The 2 ml PFS product is presented either assembled with an UltraSafe Plus passive needle guard (PFS-U) or with an YpsoMate autoinjector device (PFS-Y).

Comprehensive information on quality, manufacturing development and on the control strategy has been documented in a satisfactory manner for all presentations.

The goal of the FVP formulation development was to achieve a sterile liquid dosage form with at least 24 months shelf life at 2-8 °C. To this end, additional excipients (L-methionine and EDTA) were introduced to suppress oxidation. A formulation robustness study confirmed the adequacy of the product composition for maintaining stability under storage and shipment conditions.

Manufacturing process development is based on development efforts in parallel with the clinical development program. The manufacturing process is adequately characterised and validated. The control strategy is based on the development studies, development production campaigns, clinical production campaigns, and process validation. The quality target product profile (QTPP) was thoroughly established and used to guide the identification of CQAs. A well-founded criticality analysis of QAs was conducted. CPPs were determined for the relevant steps of procedures of FP manufacturing to ensure the best conditions for CQAs. Several phase 3 and validation batches were tested to ensure that IPCs and their respective acceptance criteria are suitable to ensure that the FP conforms to its release specifications.

The FP specification covers the aspects required as identity, purity, potency, and quantity, using adequate analytical methods. A comprehensive explanation for the setting of acceptance criteria has been provided and the criteria is overall justified. Detailed validation reports have been provided for the analytical methods used for release and stability tests of the FVP presentation, whilst the validation data on the analytical procedures approved for the 100 mg PFS has been leveraged.

The results of the stability studies support the proposed shelf life of 24 months at 2 - 8°C.

### 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The quality dossier demonstrate an adequate quality of new presentations.

### 2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- The MAH is recommended to revise the acceptance limits at release for the 10 mg/ml FVP presentation when results from 30 batches are available.

## *2.5. Non-clinical aspects*

### 2.5.1. Pharmacology

#### *2.5.1.1. Primary pharmacodynamic studies*

Two new nonclinical pharmacology studies were provided concerning the binding of guselkumab to CD64 receptors on inflammatory monocytes (Study dd24008) and the consecutive binding of IL-23 to the CD-64 receptor-guselkumab complex (Study dd24009). Flow cytometry assays reveal that guselkumab can bind to CD64+ myeloid cells in a dose-dependent manner, effectively reducing IL-23 signalling. These interactions underscore guselkumab's therapeutic potential in conditions involving excessive IL-23 activity, such as psoriasis, CD, and UC.

Further analyses indicate that the binding of guselkumab to CD64 correlates strongly with the level of CD64 expression on monocytes. Blocking experiments with anti-CD64 antibodies have shown near-complete inhibition of guselkumab binding, validating the specificity of the interaction. Additionally, guselkumab bound to CD64 on inflammatory monocytes can capture endogenous IL-23 produced by these cells, reinforcing its capability to neutralize IL-23 directly at its source of production.

#### *2.5.1.2. Secondary pharmacodynamic studies*

None.

#### *2.5.1.3. Safety pharmacology programme*

None.

#### *2.5.1.4. Pharmacodynamic drug interactions*

None.

### 2.5.2. Pharmacokinetics

None.

### 2.5.3. Toxicology

#### *2.5.3.1. Single dose toxicity*

None.

#### *2.5.3.2. Repeat dose toxicity*

In repeat-dose toxicity studies in cynomolgus monkeys, provided with the initial MAA submission guselkumab, was well tolerated at weekly doses up to 50 mg/kg IV for 5 weeks or 50 mg/kg SC for up to 24 weeks. There were no effects on cardiovascular, respiratory and nervous system function, and clinical pathology or anatomical pathology parameters.

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

- 200 mg IV Induction followed by 200 mg SC Maintenance: approximately 24 or 23 times the clinical exposure (based on Cmax or AUC, respectively) following a dose of 200 mg IV, and 62 or 44 times the clinical exposure (based on Cmax or AUC, respectively) following a dose of 200 mg SC every 4 weeks.

#### *2.5.3.3. Genotoxicity*

None.

### *2.5.3.4. Carcinogenicity*

None.

### *2.5.3.5. Reproductive and developmental 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 male guinea pigs are as follows for the proposed dosing regimen:

- 200 mg IV Induction followed by 200 mg SC Maintenance: Approximately 17 or 26 times the exposure (based on Cmax or AUC, respectively) in humans administered the 200 mg IV dose, and 63 or 45 times the exposure (based on Cmax or AUC, respectively) following the 200 mg SC maintenance dose.

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

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

- 200 mg IV Induction followed by 200 mg SC Maintenance: Approximately 9 or 12 times the exposure (based on Cmax or AUC, respectively) in humans administered the 200 mg IV induction dose, and 32 or 21 times the exposure (based on Cmax or AUC, respectively) following the 200 mg 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.

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

- 200 mg IV 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 12 or 18 times (based on Cmax or AUC, respectively) the exposure in humans administered the 200 mg IV 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) were associated with 4 to 18 times the exposure (AUC) in humans administered the 200 mg IV induction dose and 7 to 32 times the exposure (AUC) at the 200 mg maintenance dose.

### *2.5.3.6. Toxicokinetic data*

None.

### *2.5.3.7. Local tolerance*

None.

#### *2.5.3.8. Other toxicity studies*

None.

## 2.5.4. 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, gueslkumab 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).

## 2.5.5. Discussion on non-clinical aspects

Guselkumab is a human monoclonal antibody (IgG1λ) that targets IL-23 by binding to its p19 subunit, blocking its interaction with IL-23R and inhibiting subsequent signalling. This action specifically inhibits IL-23-mediated signalling without affecting IL-12 signalling. CD64+ myeloid cells have been identified as a significant source of IL-23 in inflamed tissues, such as skin lesions in psoriasis and inflamed colonic tissues in Crohn's disease and ulcerative colitis. CD64, also known as FcγRI, is a high-affinity receptor for IgG, binding monomeric IgG molecules, including guselkumab. This binding allows the antibody to neutralize IL-23 at its cellular source.

*In vitro* studies show that guselkumab inhibits IL-23-induced STAT3 phosphorylation in NKL cells and reduces IL-10 production, demonstrating its ability to block IL-23 signalling. Flow cytometry studies further demonstrate that guselkumab binds to CD64 on IFNγ-primed human monocytes in a dose-dependent manner, correlating with CD64 expression levels. Moreover, guselkumab captures IL-23 produced by these cells, indicating its potential to neutralize IL-23 at its source. Section 5.1 of the SmPC is adequately updated.

Two new pharmacology studies were performed. Study DD24008 demonstrated the Fc-dependent binding of guselkumab to CD64 on IFNγ-primed human monocytes. Study DD24009 confirmed that guselkumab binds CD64 and captures endogenous IL-23 produced by inflammatory monocytes. These non-clinical studies have confirmed guselkumab's binding to CD64 on inflammatory monocytes, highlighting its role in capturing and neutralizing locally produced IL-23. F

No new toxicology study was carried out for the new doses and administration route. However, the NOAEL values were recalculated for general repeat dose toxicity and various reproductive toxicity settings (male fertility study in guinea pigs, female fertility study in guinea pigs as well as in ePPND study in pregnant cynomolgous monkeys). 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 23 times the maximum clinical exposures following a dose of 200 mg given intravenously.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, guselkumab is not expected to pose a risk to the environment.

## 2.5.6. Conclusion on the non-clinical aspects

Guselkumab, through its specific binding to the p19 subunit of IL-23 and high-affinity interaction with CD64 on myeloid cells, effectively neutralizes IL-23 at its cellular source of inflammation. Section 5.1 of the SmPC is updated accordingly. This mechanism underscores its therapeutic potential in treating inflammatory bowel diseases where IL-23 plays a critical role.

SmPC section 5.3 is adequately updated to reflect the safety margins of the doses and route of administration used in the UC indication.

## *2.6. Clinical aspects*

### 2.6.1. Introduction

***GCP aspects***

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**

| Study ID/Phase | Participant Population | Dose Regimen | Route of Administration | Number of Participants Treated |
|---|---|---|---|---|
| QUASAR/Phase 2b (Induction Study 1) | Adult participants with moderately to severely active UC and demonstrated inadequate response or failure to tolerate conventional or advanced therapy [b] | (1) Randomized participants (1:1:1):<br>Weeks I-0, I-4, and I-8: guselkumab 400 mg IV<br>OR<br>Weeks I-0, I-4, and I-8: guselkumab 200 mg IV<br>OR<br>Weeks I-0, I-4, and I-8: Placebo IV<br>(2) Nonresponders at Week I-12:<br>(a) Guselkumab group: Weeks I-12, I-16, and I-20: guselkumab 200 mg SC *and* placebo IV<br>(b) Placebo group (crossed over): Weeks I-12, I-16, and I-20: guselkumab 200 mg IV *and* placebo SC | IV (SC) | 313 (208 guselkumab, 105 placebo) |
| QUASAR/Phase 3 (Induction Study 2) | Adult participants with moderately to severely active UC and demonstrated inadequate response or failure to tolerate conventional or advanced therapy [b] | (1) Randomized participants (3:2):<br>Weeks I-0, I-4, and I-8: guselkumab 200 mg IV<br>OR<br>Weeks I-0, I-4, and I-8: placebo IV<br>(2) Nonresponders at Week I-12:<br>(a) Guselkumab group: Weeks I-12, I-16, and I-20: guselkumab 200 mg SC *and* placebo IV<br>(a) Placebo group (crossed over): Weeks I-12, I-16, and I-20: guselkumab 200 mg IV *and* placebo SC | IV (SC) | 701 (421 guselkumab, 280 placebo) |

| | | | | |
|---|---|---|---|---|
| QUASAR/Phase 3 (Maintenance Study) | Participants with moderately to severely active UC who have demonstrated a clinical response to guselkumab (or placebo) treatment in either Induction Study 1 or Induction Study 2 | (a) Guselkumab clinical responders at Week I-12 and placebo crossover to guselkumab clinical responders at Week I-24: randomized (1:1:1) to receive the following at Week M-0 to M-44:<br>Guselkumab 100 mg SC q8w<br>OR<br>Guselkumab 200 mg SC q4w<br>OR<br>Placebo SC q4w<br>(b) Guselkumab responders at Week I-24: guselkumab 200 mg SC q4w Week M-0 to M-44<br>(c) Placebo responders at Week I-12: placebo SC q4w Week M-0 to M-44 | SC | Total: 805<br><br>Randomized (a): 568 (378 guselkumab, 190 placebo)<br><br>Nonrandomized (b+c): 237 (123 guselkumab, 114 placebo) |

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

**Bioanalytical Methods**

***Detection of Guselkumab***

A validated ECLIA method on the MSD platform (Meso Scale Discovery, Gaithersburg, MD, United States of America) was used to determine serum guselkumab concentrations in all studies submitted (QUASAR, GALAXI, GRAVITI, EDI1001, and CRD1003). The same method was used in the guselkumab PsO and PsA clinical development programs with 11 minor changes implemented.

***Detection of Antibodies to Guselkumab in Serum***

A validated ECLIA method on the MSD platform, consisting of an initial version and an updated version with improved drug tolerance, was used to detect binding antibodies to guselkumab in all studies submitted (QUASAR, GALAXI, GRAVITI, EDI1001, and CRD1003). Similarly, a non cell based ECLIA method consisting of an initial version and an updated version with improved drug tolerance was developed and validated to detect NAbs in serum samples that tested positive for binding antibodies to guselkumab.

The revised method was validated, and specific cut-points for ADA detection were established for the different populations, including healthy volunteers and participants with PsO, PsA, UC, and CD. This updated ECLIA method included a solid phase extraction and acid dissociation step to improve the drug tolerance of the assay. The method could detect 100 ng/mL of a positive control for ADA in the presence of 1000 mg/mL guselkumab in the sample, which was much higher than serum trough guselkumab concentrations (median: 50.40 µg/mL at Week 12 for IV 1,200 mg q4w and 7.71 µg/mL at

Week 24 for SC 200 mg q4w in participants from GALAXI) following IV or SC administration of guselkumab 200 mg q4w.

Samples identified as potentially positive were then tested using a specificity confirmation assay, wherein ADAs binding to labeled guselkumab competed with excess unlabeled guselkumab in the assay format described above. Potentially positive samples that demonstrated percent inhibition of assay signal at or above the confirmatory cut-point were considered to be positive for antibodies to guselkumab.

To determine the titer of positive antibody samples, samples were diluted in such a manner that the results of 2 subsequent serial 2-fold dilutions spanned the cut-point (1.56 NV). The reported titer was defined as the greatest dilution with the last potentially positive result prior to the subsequent sample result dropping below the titration cut-point.

***Detection of NAbs to Guselkumab in Human Serum***

The initial method, CP2013V-057, is a validated, non-cell-based ECLIA method to detect neutralizing anti-guselkumab antibodies in human serum samples. CP2013V-057 was previously used in the clinical studies supporting the PsO and PsA indications, but was not used in QUASAR (UC), GALAXI 2, GALAXI 3, or GRAVITI (CD).

In this method, test samples were pre-treated with acetic acid, biotinylated human IL-23 (biotin-IL-23), and an anti-human IL-23 mAb (CNTO856) to remove exogenous drug and block excess drug target IL-23 to address assay interference from circulating drug and drug target. The pre-treated samples were then incubated with biotinylated guselkumab (biotin-CNTO1959). In the absence of NAbs, biotinylated guselkumab bound to ruthenium-labeled human IL-23 (ruthenium-IL-23) and emitted an ECL signal. NAbs, when present in serum samples, competitively bound to biotinylated guselkumab and inhibited the binding of ruthenium-IL-23 to biotinylated guselkumab, resulting in a decreased ECL signal. Therefore, the level of NAb activity was inversely proportional to the measured assay signal.

As part of life cycle management, a second revised ligand-binding ECLIA method with enhanced drug tolerance, CP2020V-071, was validated to detect neutralizing anti-guselkumab antibodies in human serum samples from ADA-positive participants. The drug tolerance in CP2020V-071 was 63.07 µg/mL or 125.21 µg/mL of exogenous guselkumab when 0.5 µg/mL or 1 µg/mL of the positive NAb control, CNTO4610, was present in undiluted pooled human serum (10× final assay concentration). The assay could tolerate a maximum of 4.14 µg/mL of exogenous guselkumab when 1 µg/mL of the positive NAb control CNTO8820 was present in undiluted pooled human serum (10× final assay concentration). This revised method was used to support the clinical studies QUASAR, GALAXI, and GRAVITI.

**Comparative Bioavailability and Bioequivalence**

**Bioequivalence Study EDI1001**

The study was conducted in healthy participants to bridge the IV formulation used in QUASAR and the to-be-marketed FVP formulation for IV administration.

***Study Design:*** EDI1001 was a Phase 1, randomized, open-label, parallel-group study to assess the bioequivalence of the IV formulation of guselkumab using the 1 mL PFS-U and the IV formulation of guselkumab FVP (final vialed product) in healthy participants. One group received an IV administration of 200 mg guselkumab prepared by transferring the contents of two 1 mL (100 mg) guselkumab PFS-Us to an IV bag containing 100 mL dextrose for infusion, while a second group received 200 mg guselkumab prepared by transferring the contents of a single 200 mg FVP vial of guselkumab to an IV bag containing 250 mL 0.9% normal saline for infusion.

The total study duration for each participant was approximately 16 weeks, including a screening period of up to 4 weeks, an inpatient period of 1 week, and a follow-up period of up to 12 weeks.

***Results:*** A total of 140 healthy participants were randomly assigned to receive 200 mg guselkumab prepared from either the 1 mL PFS-U 100 mg/mL formulation or the new guselkumab 10 mg/mL FVP formulation (70 participants each). Of these, 139 participants (99.3%) completed the study, while 1 participant (0.7%) terminated study participation prematurely because of "other reason" (not related to an AE; participant relocated).

All 140 participants had at least 1 PK sample for the evaluation of guselkumab concentration while 69 participants in each group were evaluable for at least 1 PK parameter. The 2 delivery presentations also resulted in similar PK parameters of guselkumab, including $C_{max}$, $t_{max}$, $AUC_{0\text{-}85d}$, $AUC_{last}$, $AUC_{inf}$, $t_{1/2}$, CL, and $V_z$ (Table 3).

**Table 3: Summary of Guselkumab PK Parameters (CNTO1959EDI1001 Phase 1 Study; PK Analysis Set)**

| **PK Parameter** (mean [SD], $t_{max}$: median [range]) | **Group 1: 200 mg IV PFS-U** | **Group 2: 200 mg IV FVP** |
|---|---|---|
| n | 69[a] | 69[b] |
| $C_{max}$, µg/mL | 59.1 (10.6) | 58.8 (10.9) |
| $t_{max}$, day | 0.0625 (0.0592 - 5.0033) | 0.0625 (0.0592 - 0.1688) |
| $AUC_{0\text{-}85d}$, µg.day/mL | 748 (158) | 780 (178) |
| $AUC_{last}$, µg.day/mL | 743 (162) | 780 (178) |
| $AUC_{inf}$, µg.day/mL | 796 (184) | 855 (223) |
| $t_{1/2}$, day | 22.0 (5.8) | 23.8 (5.7) |
| CL, L/day | 0.264 (0.0606) | 0.249 (0.0651) |
| $V_z$, L | 8.07 (1.66) | 8.26 (1.60) |

[a] n=68 for $AUC_{0\text{-}85d}$ and n=66 for $AUC_{inf}$, CL and $V_z$.

[b] n=68 for $AUC_{inf}$, CL and $V_z$.

Table 4 summarizes the 2 co-primary PK parameters ($C_{max}$ and $AUC_{inf}$) and the GMR with its 90% CI for bioequivalence assessment.

**Table 4: Comparison of Guselkumab Cmax and AUCinf Between the PFS-U and FVP Formulations After Administration of 200 mg Guselkumab IV (CNTO1959EDI1001 Phase 1 Study; PK Analysis Set)**

| | Geometric Mean | | GMR (Test/Reference) | | |
|---|---|---|---|---|---|
| | 200 mg IV PFS-U (Reference) | 200 mg IV FVP (Test) | % | 90% CI, % | CV, % |
| N | 69[a] | 69[b] | | | |
| $C_{max}$, µg/mL | 57.9 | 57.8 | 99.77 | 94.36 - | 20.0 |
| $AUC_{inf}$, µg.day/mL | 776 | 829 | 106.76 | 99.70 - | 24.3 |

[a] n=66 for $AUC_{inf}$.

[b] n=68 for $AUC_{inf}$.

The incidence of antibody development to guselkumab was low (1.4%; 1/70) and the same for both delivery methods.

No meaningful differences were observed in AEs between the guselkumab IV administration groups (PFS-U versus FVP [IV]).

**Bioequivalence Study CRD1003**

Study CRD1003 was conducted to assess the bioequivalence of 200 mg guselkumab administered by a single SC injection using the 2 mL PFS-U or 2 mL PFS-Y and 200 mg guselkumab administered by 2 SC injections using the standard 1 mL PFS-U in healthy participants.

***Study Design:*** CRD1003 was a Phase 1, randomized, open-label, 2-part, parallel-group, adaptive design study to demonstrate the bioequivalence of 200 mg guselkumab administered SC by 3 different devices in healthy participants.

Guselkumab 200 mg SC was administered using one of the following 3 ways:

- Two SC injections of 100 mg guselkumab using the approved 1 mL PFS-U (Reference Device).
- A single SC injection of 200 mg guselkumab using the 2 mL PFS-U (Test Device 1).
- A single SC injection of 200 mg guselkumab using the 2 mL PFS-Y (Test Device 2).

CRD1003 employed an adaptive design consisting of Part 1 and Part 2. The results from Part 1 of the study were used to re-estimate the sample size for Part 2. In Part 1, approximately 42 participants were randomly assigned to each of the 3 device groups for a total of 125 participants. The PK data (GMRs and CV% of $C_{max}$ and $AUC_{inf}$ for each delivery device) were used to re-estimate the sample size for Part 2 to ensure that the sample sizes were adequate to demonstrate bioequivalence. As a result, a total of 311 healthy participants were enrolled in Part 2, with 122, 123, and 66 participants being randomly assigned to the Reference Device Group, the Test Device 1 group, and the Test Device 2 group, respectively. Across the entire study, participants were stratified by body weight (<70 kg, ≥70 to <80 kg, and ≥80 kg), randomly assigned to the appropriate groups, and followed for 12 weeks after receiving the study intervention.

Two different statistical methods were used for bioequivalence assessment to preserve adequate control of the Type I error (overall alpha level) for the bioequivalence assessment at the end of the study:

1. Two 1-sided tests procedure: the estimated sample sizes in Part 1 and Part 2 were used to prespecify the weights for Part 1 and Part 2, and a weighted sum of test statistics was used for the bioequivalence testing at the end of the study. Bioequivalence was to be declared if: $T_U^* < -t_{1-\alpha,df}$ and $T_L^* > t_{1-\alpha,df}$ for both $AUC_{inf}$ and $C_{max}$, where $t_{1-\alpha,df}$ is the critical value based on the degrees of freedom of combined test statistics T* and would be different between the device comparisons and PK parameters.
2. Repeated confidence interval method: compared with the Reference Device (2×1 mL PFS-U), if the 90% RCIs of the GMRs for $C_{max}$ and $AUC_{inf}$ for both Test Device 1 (1×2 mL PFS-U) and Test Device 2 (1×2 mL PFS-Y) fell within the bioequivalence interval of 80.00% to 125.00%, bioequivalence was to be declared.

***Results*:** Of all 440 randomly assigned participants, 4 participants were not treated because of early termination prior to dose administration. Thus, a total of 436 healthy participants either from the Reference Device (2×1 mL PFS-U; n=164), Test Device 1 (1×2 mL PFS-U; n=165), or Test Device 2 (1×2 mL PFS-Y; n=107) group were included in the safety and PK analysis sets. One additional participant in the Reference Device Group received guselkumab but discontinued the study before $C_{max}$ was reached; this participant was excluded from the PK analysis because the insufficient serum concentration data did not allow for accurate assessment of the PK parameters.

The demographic and baseline characteristics were comparable across participants from the 3 device groups (ie, median body weight was 73.4, 73.9, and 75.1 kg, respectively, for Reference Device, Test Device 1, and Test Device 2).

The PK parameters are provided in Table 5.

**Table 5: PK Results After 200 mg SC Administration of Guselkumab in Healthy Participants with Reference Device (2×100 mg in 1 mL PFS-U), Test Device 1 (1×200 mg in 2 mL PFS-U), and Test Device 2 (1×200 mg in 2 mL PFS-Y) (CNTO1959CRD1003 Phase 1 Study; PK Analysis Set*)***

| **PK Parameter** (mean [SD], $t_{max}$: median [range]) | **Reference Device 2×1 mL PFS-U** | **Test Device 1 1×2 mL PFS-U** | **Test Device 2 1×2 mL PFS-Y** |
|---|---|---|---|
| N | 155[a] | 163[b] | 106[c] |
| $C_{max}$, µg/mL | 16.7 (5.21) | 14.8 (4.62) | 15.9 (4.48) |
| $t_{max}$, day | 5.00 (1.98 - 14.99) | 5.00 (2.00 - 14.04) | 5.00 (2.00 - 14.01) |
| $AUC_{0\text{-}85d}$, µg.day/mL | 493 (169) | 428 (150) | 463 (148) |
| $AUC_{last}$, µg.day/mL | 493 (169) | 428 (150) | 463 (148) |
| $AUC_{inf}$, µg.day/mL | 526 (192) | 459 (170) | 491 (164) |
| $t_{1/2}$, day | 19.6 (4.2) | 20.1 (4.8) | 19.1 (4.0) |
| CL/F, L/day | 0.442 (0.202) | 0.521 (0.296) | 0.455 (0.159) |
| $V_z$/F, L | 11.9 (4.29) | 14.1 (5.67) | 12.1 (3.48) |

[a] n=154 for $AUC_{0\text{-}85d}$ and $AUC_{last}$, n=153 for $AUC_{inf}$, CL/F, and $V_z$/F, n=160 for $t_{1/2}$.

[b] n=160 for $AUC_{0\text{-}85d}$ and $AUC_{last}$, n=161 for $AUC_{inf}$, CL/F, and $V_z$/F.

[c] n=105 for $AUC_{0\text{-}85d}$ and $AUC_{last}$, $AUC_{inf}$, $t_{1/2}$, CL/F, and $V_z$/F.

Bioequivalence was calculated with WinNonLin.

Bioequivalence Inferential Results via RCIs of Study CRD1003 pharmacokinetic results are provided in Table 6.

**Table 6: Bioequivalence Inferential Results via RCIs (CNTO1959CRD1003 Phase 1 Study; PK Analysis Set)**

| **Bioequivalence Test** (GMR [90% CI]) | **PK Parameter** | **Part 1** | **Part 2** | **Combined** |
|---|---|---|---|---|
| **Test Device 1 (2 mL PFS-U)/ Reference** | $AUC_{inf}$ | 87.32 (76.48 - 99.69) | 87.05 (80.51 - 94.12) | 87.15 (81.93 - 93.58) |
| | $C_{max}$ | 87.74 (77.13 - 99.82) | 87.96 (81.90 - 94.47) | 87.88 (82.24 - 93.91) |
| **Test Device 2 (2 mL PFS-Y)/ Reference** | $AUC_{inf}$ | 91.25 (81.21 - 102.52) | 99.99 (91.75 - 108.98) | 96.34 (89.71 - 103.46) |
| | $C_{max}$ | 95.31 (85.03 - 106.84) | 97.41 (89.90 - 105.56) | 96.56 (90.24 - 103.32) |

RCI calculated according to Lehmacher (1999)[a].

Upon the CHMP's request, the MAH provided additional BE evaluation with an appropriate multiplicity adjustment:

**Table 7: Bonferroni-adjusted Confidence Intervals**

| Test Device | PK Parameters | 95% Confidence Intervals |
|---|---|---|
| 1×2.0 mL PFS-U | AUC | 87.15 (80.06, 94.87) |
| | $C_{max}$ | 87.88 (81.20, 95.11) |
| 1×2.0 mL PFS-Y | AUC | 96.34 (88.49, 104.89) |
| | $C_{max}$ | 96.56 (89.08, 104.66) |

Abbreviations: AUC=area under the serum concentration versus time curve; $C_{max}$=maximum observed serum concentration; PFS-U=prefilled syringe assembled with the UltraSafe Plus™ Needle Guard; PFS-Y=prefilled syringe assembled with the YpsoMate™ Autoinjector; PK=pharmacokinetic.

Of the 432 participants evaluable for immunogenicity, 4.3% (7 of 162), 3.0% (5 of 164), and 6.6% (7 of 106) were positive for antibodies to guselkumab through Week 12 for the Reference Device (2×1 mL PFS-U), Test Device 1 (1×2 mL PFS-U), and Test Device 2 (1×2 mL PFS-Y), respectively.

Study intervention was administered SC in the front, upper portion of the thigh. When 2 injections were administered (2×1 mL PFS-U), injections were made bilaterally. No clinically relevant differences

[a] 6. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999;55(4):1286–1290.

in PK exposures are expected for mAbs following SC injections at different injection sites (ie, the thigh, abdomen, and upper arm [Xu 2010[a]; Anumolu 2018[b]; Shabbir 2020[c]]). Study results from CRD1003 in which the front upper portion of the thigh was chosen as the injection site are also considered to be reflective of injections using other injection sites, including the abdomen and the upper arm.

**QUASAR study**

The QUASAR study is designed to evaluate the efficacy and safety of guselkumab in the treatment of moderately to severely active UC. The study had three parts: Phase 2b induction dose-ranging study (Induction Study 1, hereafter IS-1) and 2 Phase 3 studies (Induction Study 2, hereafter IS-2, and the randomized-withdrawal Maintenance Study). In each part of Study QUASAR, serum samples were collected to determine guselkumab and antibodies to guselkumab concentrations to characterize the pharmacokinetics in the target population and to describe the concentration- efficacy and concentration–safety relationships.

An overview of the design and conduct of IS-1 and IS-2 is presented in the Clinical Efficacy Section 2.6.5.1. .

***Serum Guselkumab Concentrations Through Week I-12***

Following IV administration of 200 mg guselkumab at Weeks I-0, I-4, and I-8, median (mean) serum guselkumab concentrations at 1 hour post IV infusion at Weeks I-0, I-4, and I-8 were 60.02 (61.65) µg/mL, 65.40 (67.23) µg/mL, and 66.64 (68.42) µg/mL, respectively. At Week I-12, the timepoint of the primary endpoint in IS-2, the median (mean) $C_{trough}$ was 9.37 (10.15) µg/mL.

***Body weight***

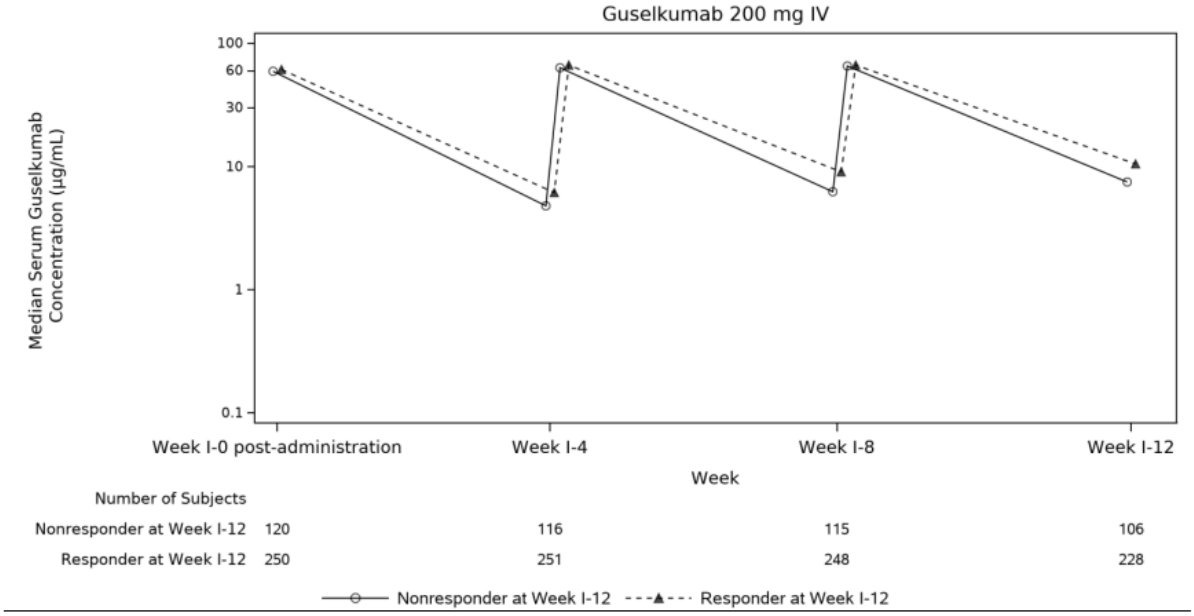
Following IV induction of 200 mg guselkumab at Weeks I-0, I-4 and I-8, median serum guselkumab concentrations tended to decrease with increasing body weight through Week I-12. At Week I-12, the median trough guselkumab concentrations were 11.2 µg/mL, 10.8 µg/mL, 8.5 µg/mL, and 7.2 µg/mL for participants with baseline body weight <1st quartile, ≥1st and <2nd quartile, ≥2nd and <3rd quartile, and ≥3rd quartile, respectively (1st quartile = 60.0 kg, 2nd quartile = 71.3 kg, and 3rd quartile = 83.7 kg).

***Clinical Nonresponders***

Line plot of median serum guselkumab concentrations through Week I-12 by clinical response status is provided in Figure 1.

[a] Xu Z, Wang Q, Zhuang Y, et al. Subcutaneous bioavailability of golimumab at 3 different injection sites in healthy subjects. J Clin Pharmacol. 2010;50(3):276–284.
[b] Anumolu SS, Lindgren S, Vemula J, et al. Bioequivalence of canakinumab injected subcutaneously via an autoinjector device or
[c] Shabbir S, Pouliquen IJ, Bentley JH, Bradford ES, Kaisermann MC, Albayaty M. The pharmacokinetics and relative bioavailability of mepolizumab 100 mg liquid formulation administered subcutaneously to healthy participants: a randomized trial. Clin Pharmacol Drug Dev. 2020;9(3):375–385.

**Figure 1: GPKCONC503: Line Plot of Median Serum Guselkumab Concentrations (microgram/mL) Through Week I-12 by Clinical Response Status at Week I-12; Pharmacokinetics Analysis Set (Study CNTO1959UCO3001; Induction 2)**




Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
(1) Concentrations below the lowest quantifiable concentration (ie, <0.01 µg/mL) were treated as zero in calculating the summary statistics.
[gpkconc503.rtf] [cnto1959/uco3001/dbr_inducs2_w32/re_w32/gpkconc503.sas] 10JUL2023, 16:01

**Comparison of serum guselkumab concentrations between IS-1 and IS-2**

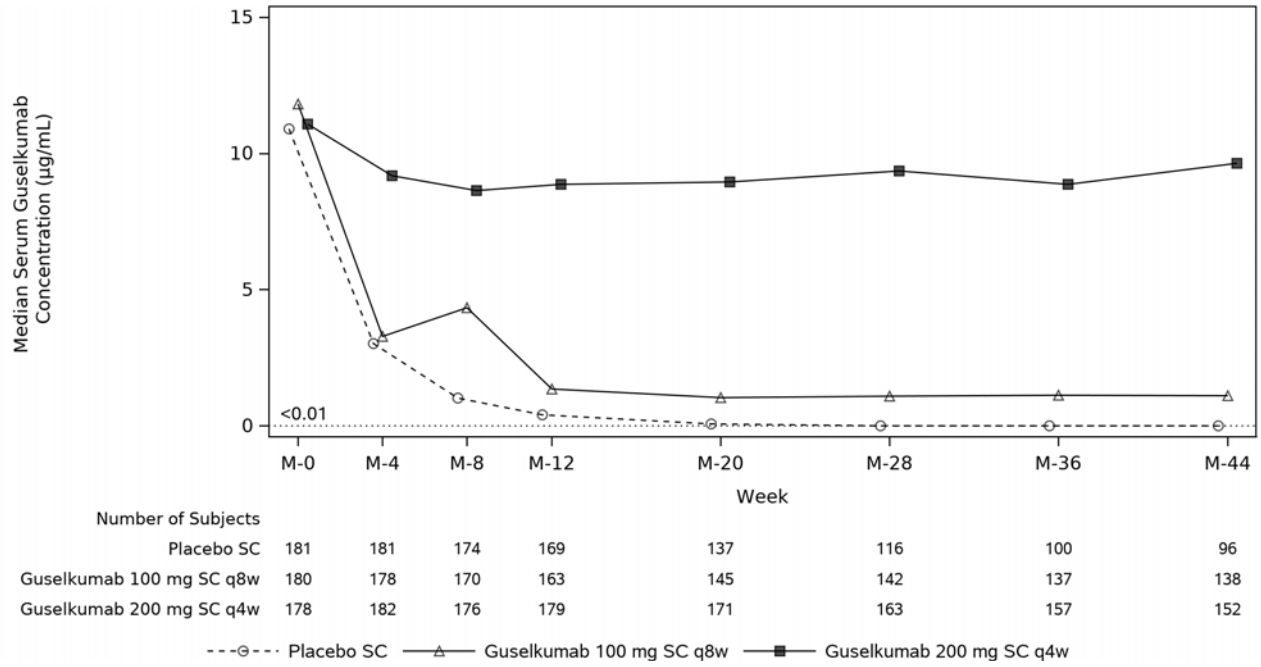
Serum guselkumab concentrations over time following 200 mg IV were consistent between IS-1 and IS-2. Following IV induction with guselkumab 200 mg (using pooled data from IS-1 and IS-2), the median (mean) serum peak guselkumab concentrations at 1 hour post IV infusion at Weeks I-0, I-4, and I-8 were 59.90 (62.39) µg/mL, 65.04 (67.06) µg/mL, and 66.26 (68.27) µg/mL, respectively. At Week I-12, the median (mean) $C_{trough}$ was 9.45 (10.26) µg/mL for the combined guselkumab 200 mg IV group from IS-1 and IS-2.

**Maintenance Study**

For serum guselkumab, determination predose samples were collected at all dosing visits before the SC study intervention administration.

Serum guselkumab concentrations reached steady-state at approximately Week M-8 and Week M-12 following maintenance treatment with guselkumab 200 mg SC q4w and 100 mg SC q8w, respectively (Figure 2).

**Figure 2: Line Plot of Median Serum Guselkumab Concentrations (µg/mL) Through Week M-44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized PK Analysis Set)**




Week M-44=maintenance week 44.

At Week M-44, the median (mean) steady state Ctrough was 9.65 (10.67) µg/mL and 1.10 (1.36) µg/mL for the 200 mg SC q4w group and 100 mg SC q8w group, respectively.

***Serum Guselkumab Concentrations Through Week M-44 by Baseline Body Weight***

Following guselkumab SC maintenance dose, median $C_{trough}$ tended to decrease with increasing body weight quartiles in each guselkumab treatment group. Following the treatment with guselkumab 100 mg SC q8w, which started at Week M-4, the median (mean) $C_{trough}$ at Week M-44 were 1.84 (2.04) µg/mL, 1.23 (1.27) µg/mL, 1.00 (1.26) µg/mL, and 0.77 (0.96) µg/mL for participants with induction baseline body weight in the first to the fourth quartile (<58.20 kg, ≥58.20 kg to <68.75 kg, ≥68.75 kg to <83.50 kg, and ≥83.50 kg, respectively). A similar trend was observed in the 200 mg group.

***Serum Guselkumab Concentrations Through Week M-44 in Participants who Had a Dose Adjustment***

Among participants randomized to the guselkumab 100 mg SC q8w group, serum guselkumab concentrations were lower in participants who met the criteria for loss of response compared with those who did not meet the criteria. At Week M-0, the median (mean) serum guselkumab concentration in participants (n=19) who were later dose-adjusted to 200 mg SC q4w was 8.16 (9.58) µg/mL compared with 12.46 (13.36) µg/mL in participants (n=161) who did not dose-adjust. A similar pattern was observed at other timepoints through Week M-12 for these 2 subgroups. At Week M-12, the steady-state median serum guselkumab concentrations were approximately 50% lower in participants (n=14) who had dose adjustment compared with those (n=149) who did not dose-adjust (0.70 µg/mL vs 1.41 µg/mL). Comparisons cannot be made after Week M-12 because there were too few participants who had dose adjustment at the scheduled PK collection visits (ie, Weeks M-20 and M-28) before Week M-32.

Serum guselkumab concentrations increased following dose adjustment from guselkumab 100 mg SC q8w to guselkumab 200 mg SC q4w. The median (mean) average $C_{trough}$ increased from 0.73 (0.86) µg/mL prior to dose adjustment to 6.51 (7.12) µg/mL after dose adjustment in these participants.

In contrast to the observations for the participants in the guselkumab 100 mg SC q8w guselkumab group, among participants randomized to the guselkumab 200 mg SC q4w group, serum guselkumab concentrations were similar between participants who met the criteria for loss of response and those who did not meet the criteria. From Week M-12 to Week M-44, participants who were dose-adjusted had median serum guselkumab concentrations of 8.38 to 9.68 µg/mL, which were similar to the concentrations of 8.68 to 9.68 µg/mL in participants who did not meet the criteria for loss of response/dose-adjustment.

Among participants randomized to the placebo SC group, serum guselkumab concentrations increased following dose adjustment from placebo SC to guselkumab 200 mg SC q4w; the median (mean) value of average $C_{trough}$ increased from 0.17 (0.38) µg/mL to 7.84 (8.91) µg/mL.

***Serum Guselkumab Concentrations Through Week M-44 in Guselkumab Week I-24 Responders***

Participants who were not in clinical response at Week I-12 following guselkumab 200 mg IV or 400 mg IV induction treatment received guselkumab 200 mg SC q4w at Weeks I-12, I-16, and I-20 in IS-1 or IS-2. If they were in clinical response at Week I-24 (referred to as guselkumab Week I-24 responders), they continued to receive guselkumab 200 mg SC q4w during the Maintenance Study. Accordingly, Week I-24 of the induction study corresponds to Week M-0 of the Maintenance Study for guselkumab Week I-24 responders.

Steady-state serum guselkumab concentrations were reached at approximately Week M-0 in guselkumab Week I-24 responders. Median serum concentrations at pre-administration timepoints during the Maintenance Study in this group ranged between 6.97 to 8.64 µg/mL following administration of guselkumab 200 mg SC q4w.

Guselkumab Week I-24 responders had lower median serum guselkumab concentrations than guselkumab IV induction responders following maintenance treatment of guselkumab 200 mg SC q4w. Participants who were randomized to guselkumab 200 mg SC q4w reached guselkumab steady-state concentrations at approximately Week M-8, by which time the impact of the IV induction doses was diminished. Thus, it is appropriate to compare guselkumab concentrations from Week M-8 onward. Median steady-state $C_{trough}$ ranged from 8.63 to 9.65 µg/mL among guselkumab IV induction responders compared with 7.50 to 8.64 µg/mL among guselkumab Week I-24 responders from Week M-8 through Week M-44.

***ADT status***

Median serum guselkumab concentrations through Week M-44 tended to be lower in participants who had previously failed or who were intolerant to ADT (ie, TNF$\alpha$ antagonists, vedolizumab, tofacitinib) than participants who had not previously failed an ADT.

**Population PK Analysis in Participants With Active UC**

A total of 10,115 measurable serum guselkumab concentrations from 859 adult participants of the QUASAR Induction and Maintenance Studies with active UC and a modified Mayo score of 5 to 9 at induction baseline who received at least 1 guselkumab dose and who had at least 1 valid PK measurement in the QUASAR Induction and Maintenance Studies were included in the population PK analysis.

The participants in the final population PK dataset (n=859) had a median age of 39 years (range: 18 to 84 years) and a median body weight of 70.5 kg (range: 36 to 148 kg). Most of the participants were male (n=499, 58.1%) and Caucasian (n=609, 70.9%). Elderly participants included 52 (6.1%) with an age ≥65 years and 9 (1.04%) with an age ≥75 years. Of the 859 participants, 69.5% (n=597) had normal renal function (ie, eGFR ≥90 mL/min), 28.5% (n=245) had mild renal impairment (ie, eGFR 60

to 90 mL/min), and 2.0% (n=17) had moderate renal impairment (ie, eGFR 30 to 60 mL/min) at induction baseline. There were no participants with severe renal impairment (ie, eGFR <30 mL/min). Around 3.0% (n=26) and 1.7% (n=15) of the participants had abnormal liver ALT and AST enzyme levels (ie, ≥1×ULN) at induction baseline, respectively. Approximately half of the participants (51.6%) had not failed biologics previously. Participants' median disease duration was 5.39 years (range: 0.3 to 47.7 years); the median modified Mayo score at induction baseline was 7 (range: 5 to 9). Approximately 70% and 30% of the participants had endoscopy subscores of 3 (severe activity) and 2 (moderate activity), respectively, and 47.0% of the participants had extensive UC disease (ie, affecting the entire colon). Concomitant immunomodulators (ie, AZA, 6MP, MTX) were used by 21.0% of participants at induction baseline; 44.9% of participants received corticosteroids at induction baseline. A total of 6.7% (58/859) of participants had treatment-emergent antibodies to guselkumab.

The guselkumab serum concentration-time profile in UC participants were adequately described by a 2-compartment linear PK model with first-order absorption and first-order elimination. The final population PK parameter estimates along with estimates of the included covariate effects are summarized in Table 8.

Model parameters were estimated well with RSEs less than 20% for most parameters. A stable covariate model was developed, which included the covariate effects of body weight, baseline serum albumin, baseline CRP, baseline eGFR, biologic failure status, and sex on CL, and body weight on V2 and V3. Other covariates tested were not statistically significant. eGFR was replaced with age in the final model due to the correlation between age and eGFR (r=0.4). In addition, mAb disposition is usually not affected by renal function and hence age was chosen instead of eGFR in the final model in view of the above-mentioned correlation between both covariates.

The final population PK model was used to simulate post-hoc exposures and construct forest plots for assessing covariate effects on simulated post-hoc exposure metrics during the induction ($C_{trough,week12}$) with a fixed induction dose regimen of 200 mg IV q4w and during the Maintenance Study ($C_{trough,week44}$) with a fixed maintenance dose regimen of 200 mg SC q4w.

The covariate effects in forest plots were represented as point estimates of the GMR and associated 90% CIs. Compared with the reference value or level, statistically significant covariates from the final PK model (body weight, age, baseline serum albumin, baseline CRP, sex, and biologic failure status) had no clinically relevant impact on $C_{trough}$ during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

**Table 8: Parameter Estimates in the Final Population PK Model for Guselkumab in Participants With Moderately to Severely Active UC**

| Parameters | Estimate[a] | 95% CI | Magnitude of Change[c] |
|---|---|---|---|
| CL (L/day) [b] | 0.312 (1.82) | (0.301, 0.323) | -- |
| BWT on CL | 0.538 (8.42) | (0.449, 0.627) | -18.3% to +22.5% |
| ALB on CL | -1.17(13.3) | (-1.48, -0.864) | +23.1% to -14.2% |
| CRP on CL | 0.0365 (21.3) | (0.0213, 0.0517) | -8.2% to +8.2% |
| AGE on CL | -0.0741 (40.4) | (-0.133, -0.0155) | 4.69% to -3.83% |
| FBIO on CL | 0.108 (19.1) | (0.0676, 0.148) | +10.8% |
| SEX on CL | -0.111 (15.9) | (-0.146, -0.0763) | -11.1% |
| Q (L/day) | 0.298 (8.96) | (0.246, 0.350) | - |
| V2 (L) [c] | 3.38 (0.757) | (3.33, 3.43) | - |
| BWT on V2 | 0.512 (5.72) | (0.455, 0.569) | -17.5% to +21.3% |
| V3 (L) [d] | 2.58 (4.19) | (2.37, 2.79) | - |
| BWT on V3 | 0.512 (5.72) | (0.455, 0.569) | -17.5% to +21.3% |
| $k_a$ (1/day) | 0.123 (8.02) | (0.104, 0.142) | - |
| F1 | 0.588 (3.33) | (0.550, 0.626) | - |
| IIV of CL (CV%) | 25.9% (3.05) [3.34][b] | (25.9%, 26.7%) | - |
| IIV of V2 (CV%) | 18.1% (4.42) [17.5][b] | (17.8%, 18.7%) | - |
| IIV of V3 (CV%) | 25.6% (7.24) [32.1][b] | (24.6%, 27.4%) | - |
| IIV of F1 (CV%) | 31.2% (4.41) [24.6][b] | (30.6%, 31.7%) | - |
| Proportional residual error | 0.193 (2.43) | (0.184, 0.202%) | - |
| Additive residual error (µg/mL) | 0.0182 (39.3) | (0.00417, 0.0322) | - |

AGE=baseline age (years); ALB=baseline serum albumin (g/L); BWT=baseline body weight (kg) ; CI=confidence interval; CL=clearance; CRP=C-reactive protein (mg/L); CV=coefficient of variation; F1=absolute bioavailability; FBIO=biologic failure status (0=no failure, 1=failure); IIV=interindividual variability, calculated as (variance)$^{1/2}$*100% except for IIV on F1 (logit scale parameter), which is calculated as (variance)$^{1/2}$*(1-THETA.F1)*100%; $k_a$=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling; PK=pharmacokinetics; PopPK=population PK; Q=intercompartmental flow; RSE=relative standard error; SEX=sex (0=male, 1=female); UC=ulcerative colitis; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] Mean (RSE%) [Shrinkage %] estimates by NONMEM from the final PK analysis dataset.

[b] $CL\left(\frac{L}{day}\right) = 0.312 \times \left(\frac{BWT}{70}\right)^{0.538} \times \left(\frac{ALB}{43}\right)^{-1.17} \times \left(\frac{CRP}{4.28}\right)^{0.0365} \times \left(\frac{AGE}{39}\right)^{-0.0741} \times 1.108^{FBIO} \times 0.889^{SEX}$

[c] $V2(L) = 3.38 \times \left(\frac{BWT}{70}\right)^{0.512}$

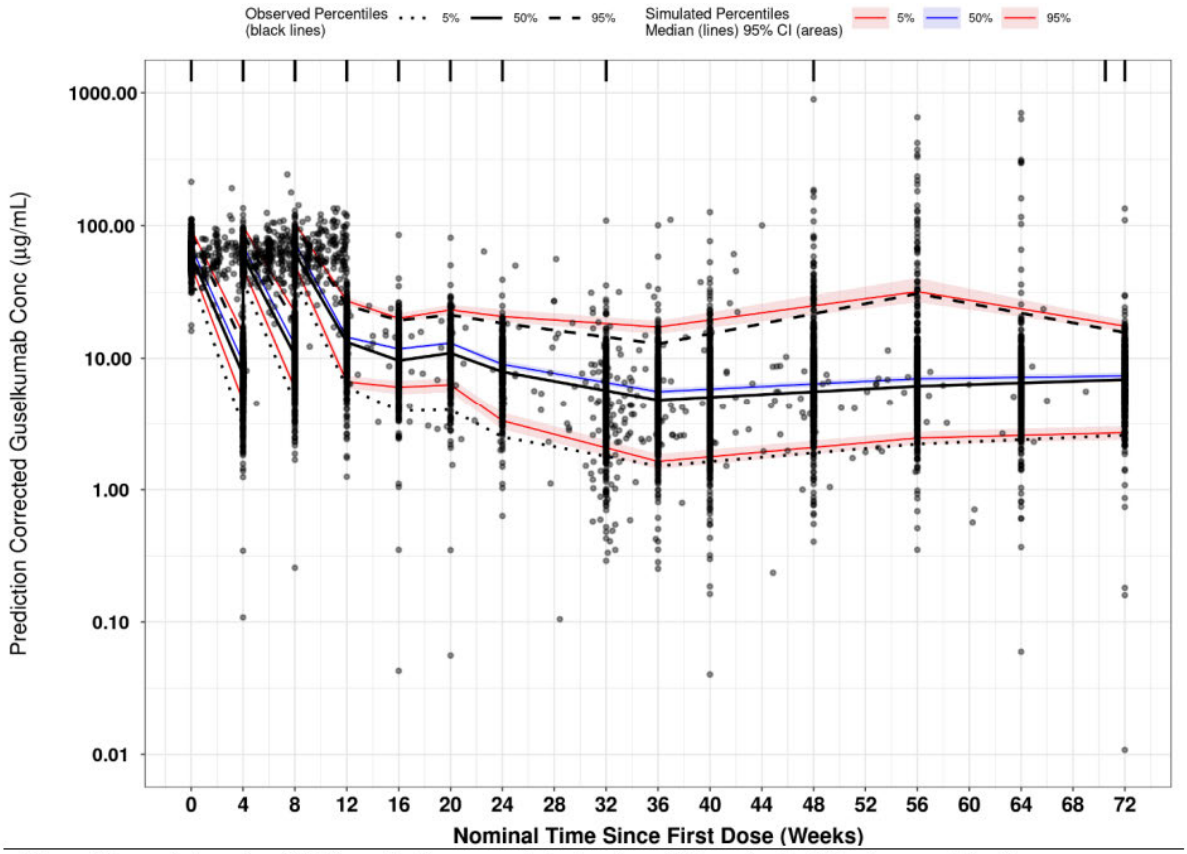
[d] $V3(L) = 2.58 \times \left(\frac{BWT}{70}\right)^{0.512}$

[e] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from the 5$^{th}$ percentile to the 95$^{th}$ percentile of the population.

**Model Evaluation**

The performance of the final PopPK model was evaluated using pcVPC (N=1,000 replicates) (Figure 3).

**Figure 3: Predicted Corrected Visual Predictive Check (pcVPC) for the Final PopPK Model**

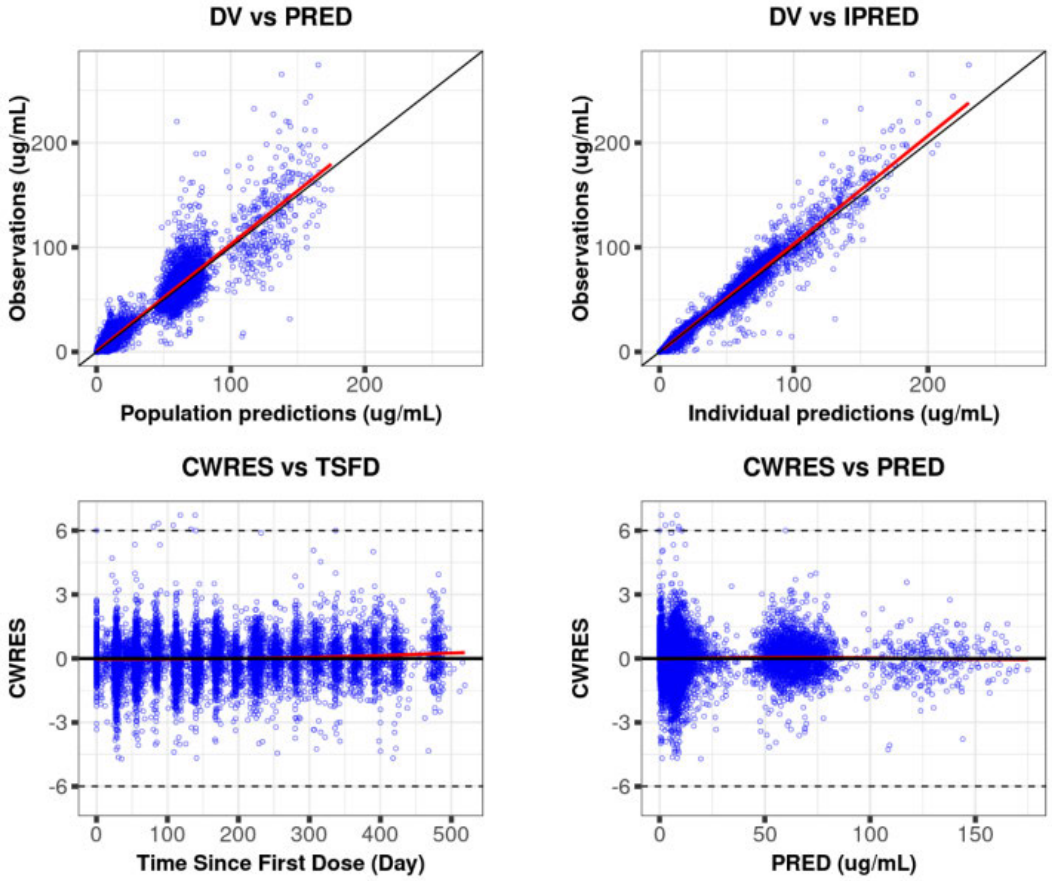



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; PopPK=population PK.

Black solid and dotted/dashed lines are the 50th and 5th/95th percentile of the observations. Blue and red solid lines are the 50th and 5th/95th percentile of the model predictions. Blue areas are the 90% CI of the simulated median trend. Red areas are the 90% CI of the simulated trends at 5th and 95th percentiles.

The standard diagnostic plots were generated to evaluate the adequacy of the base and final covariate models. Plots of observed guselkumab concentrations versus population predicted and individual predicted concentrations and scatter plots of weighted residuals and conditional weighted residuals versus predicted data and time elapsed from the beginning of the first dose or time elapsed from the most recent dose are provided in Figure 4.

**Figure 4: Plots of observed guselkumab concentrations versus population predicted and individual predicted concentrations and scatter plots of weighted residuals and conditional weighted residuals versus predicted data and time elapsed from the beginning of the first dose or time elapsed from the most recent dose**




CWRES=conditional weighted residuals; DV=dependent value or observation; GOF=goodness-of-fit; IPRED=individual predictions; PK=pharmacokinetics; PRED=population predictions; TSFD=time since first dose. The black solid line is the line of identity or the zero line, and the red dashed line is the trend line. The blue circles are the observations.

**Effect of Intrinsic Factors**

**Effect of Demographic Covariates**

**Effect of Body Weight**

Body weight was a statistically significant covariate identified for CL, V2, and V3 of guselkumab in the final population PK model. The mean and median body weight of the 859 participants included in the population PK analysis were 72 kg and 70.5 kg, respectively (range: 36 to 148 kg). The model-predicted values of CL, V2, V3, and Q increased as body weight increased.

The change in CL due to body weight ranged from -18.3% to +22.5% relative to the median CL estimate when body weight increased from the 5$^{th}$ percentile (48.1 kg) to the 95$^{th}$ percentile (102.1 kg) of the population values. The change in V2 and V3 attributable to weight ranged from -17.5% to +21.3% relative to the median V2 and V3 estimate when body weight increased from the 5$^{th}$ to the 95$^{th}$ percentile.

Participants in different body weight ranges showed consistent clinical efficacy.

**Effect of Age**

Age was a statistically significant covariate for CL in the final population PK model. Participants' mean and median age was 40.9 years and 39 years, respectively (range: 18 to 84 years). Participants older than the median age had lower CL. The change in CL attributed to age ranged from +4.69% to -3.83% relative to the median CL estimate when age increased from the 5$^{th}$ (21 years) to the 95$^{th}$ percentile (66 years) of the population values.

Age had no clinically relevant impact on the simulated guselkumab exposures ($C_{trough}$ or $C_{ave}$) during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

In addition, the guselkumab exposures in the elderly participants (≥65 years) were not meaningfully different from those in younger participants (<65 years).

**Effect of Sex**

Sex was a statistically significant covariate for CL in the final population PK model. Of the 859 participants in the analysis, 360 (41.9%) were female. The model-predicted mean CL values for guselkumab were approximately 11% lower in female participants than in male participants after accounting for the effect of body weight.

Sex had no clinically relevant impact on the simulated guselkumab exposures ($C_{trough}$ or $C_{ave}$) during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

**Effect of Race and Ethnicity**

Based on the data with a limited number of participants (N=9, Black) from races other than Caucasian (N=609) and Asian (N=188), race had no statistically significant impact on the CL of guselkumab. As compared with non-Chinese and non-Japanese participants, simulated guselkumab exposure in Chinese and Japanese participants during both Induction and Maintenance Studies were not statistically different.

**Effect of Induction Baseline Serum Albumin**

Serum albumin level was a statistically significant covariate for CL in the final population PK model. Participants with baseline serum albumin levels lower than the median value (43 g/L) had a higher CL.

Participants' mean and median serum albumin levels were 42.8 g/L and 43.0 g/L, respectively (range: 16 to 55 g/L). The change in CL attributed to albumin ranged from +23.1% to -14.2% relative to the median CL estimate when albumin increased from the 5$^{th}$ percentile (36 g/L) to the 95$^{th}$ percentile (49 g/L) of the population values.

Baseline serum albumin had no clinically relevant impact on the simulated guselkumab exposures ($C_{trough}$ or $C_{ave}$) during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

The assessment of the effect of hypoalbuminemia on guselkumab exposures is limited because the majority (>97%) of the participants had serum albumin levels greater than 35 g/L at induction baseline.

**Effect of Other Laboratory Characteristics**

None of the other laboratory characteristics assessed as potential covariates (ALP, ALT, and AST; total bilirubin; platelets and white blood cell counts) had a statistically significant impact on the CL of guselkumab.

**Effect of Induction Baseline Disease Characteristics**

Participants' disease duration, modified Mayo score at induction baseline, and Mayo endoscopy subscore at baseline were evaluated as potential covariates for CL in the population PK analysis. None of these disease characteristics had a statistically significant impact on the CL of guselkumab.

**Effect of Induction Baseline Inflammatory Biomarkers**

**Effect of C-reactive Protein**

Serum CRP level was a statistically significant covariate for CL in the final population PK model. Participants' mean and median CRP levels were 9.2 mg/L and 4.28 mg/L, respectively (range: 0.1 to 113 mg/L). The change in CL attributed to CRP ranged from -8.2% to +8.2% relative to the median CL estimate when CRP increased from the $5^{th}$ percentile (0.41 mg/L) to the $95^{th}$ percentile (37.4 mg/L) of the population values.

Induction baseline CRP had no apparent impact on the simulated guselkumab exposures ($C_{trough}$ or $C_{ave}$) during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

**Effect of Fecal Calprotectin**

Fecal calprotectin levels at induction baseline had no statistically significant impact on the CL of guselkumab.

**Effect of Immunogenicity**

Participants' ADA status to guselkumab had no statistically significant impact on the CL of guselkumab.

**Effect of Extrinsic Factors**

**Effect of Failure to Prior ADT or Biologics Status**

In the univariate analysis, ADT failure status and biologic failure status had similar effects on CL, but only biologic failure status was retained in the stepwise covariate evaluation process because ADT failure status was highly correlated with biologic failure status (r=0.98). Of all 859 participants, 416 (48.4%) had a treatment failure of prior biologics. The model-predicted mean CL values for guselkumab were approximately 10.8% higher in participants who had biologic failure than in the participants who did not.

Biologic failure status had no clinically relevant impact on the simulated guselkumab exposures ($C_{trough}$ or $C_{ave}$) during both Induction and Maintenance Studies, because either the point estimates or the upper/lower end of their associated 90% CIs fell within the range of 0.8 to 1.25.

**Effect of Concomitant Therapies**

Concomitant use of immunomodulators (ie, AZA, 6-MP, MTX) and concomitant use of corticosteroids were evaluated as potential covariates for the PK of guselkumab. Neither had a statistically significant impact on the CL of guselkumab.

**Effect of Concurrent Comorbidity**

The medical history of diabetes was evaluated as potential covariate for the PK of guselkumab. Diabetes history had no statistically significant impact on the CL of guselkumab.

**Effect of Smoking Status**

Current smoking status was evaluated as potential covariate for the PK of guselkumab. Smoking status had no statistically significant impact on the CL of guselkumab.

***Special populations***

**Table 9: Number of Participants Aged ⩾65 Years in the PopPK Analysis Population in Study CNTO1959UCO3001**

| | Age 65-74 Years (Older Participants Number/ Total Number) | Age 75-84 Years (Older Participants Number/ Total Number) | Age ≥85 Years (Older Participants Number/ Total Number) |
|---|---|---|---|
| PK studies | 43 / 859 | 9 / 859 | 0 / 859 |

Abbreviations: PK=pharmacokinetic; PopPK=population pharmacokinetics.

Note: A total of 859 participants with a baseline modified Mayo score of 5-9 who received at least 1 guselkumab dose and had at least 1 measurable guselkumab concentration were included in the PopPK analysis.

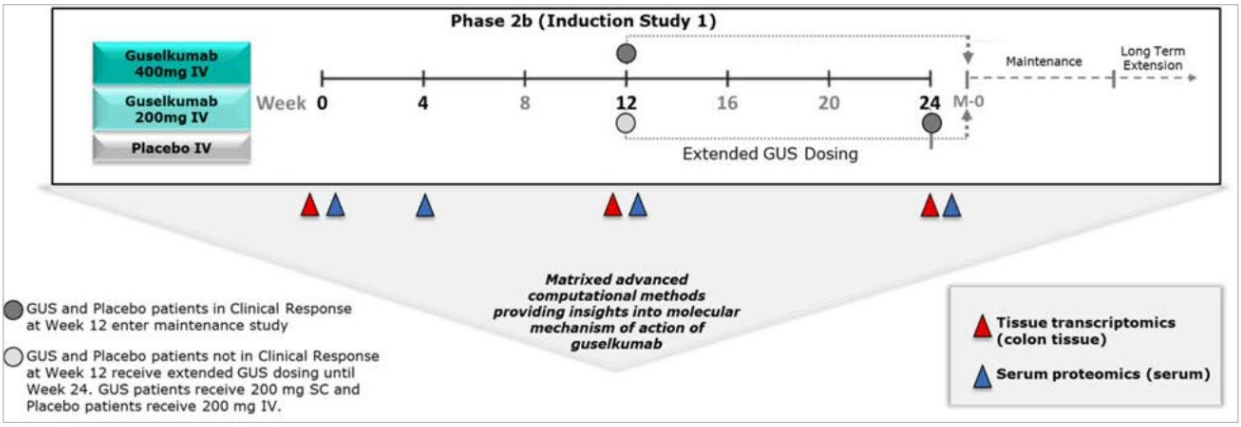
### *2.6.2.2. Pharmacodynamics*

***Biomarkers***

The pharmacodynamic response of guselkumab in relation to IL-17A, IL-22 and IFNγ, key effector cytokines associated with the IL-23 pathway and UC was assessed by serum proteomics and RNA transcriptional profiling of colon tissue.

Serum and colonic biopsy samples were collected from all participants of Study Quazar das displayed in Figure 5.

**Figure 5: Biomarker sample collection depiction within Phase2b study design**

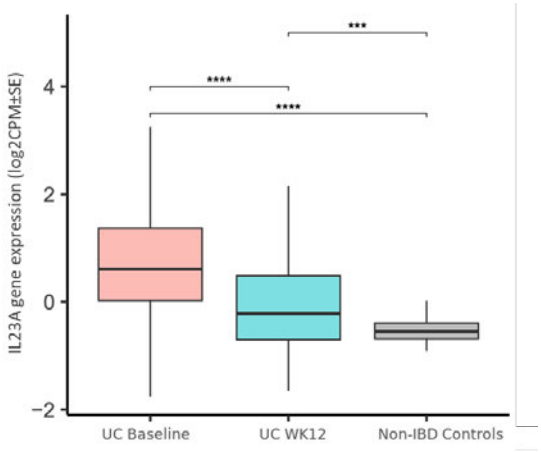



**Tissue Transcriptomics**

IL-23p19 (IL23A) gene expression is elevated in UC colon tissue at baseline relative to non-IBD control tissue.

The data on tissue gene expression of IL-23 (IL23A) with guselkumab treatment at Week I-12 are provided in Figure 6.

**Figure 6: Gene Expression of IL-23 (IL23A) in Colon Tissue; Randomized Analysis Set (Study CNTO1959UCO3001; Induction Study 1)**




Abbreviations: CPM=counts per million; IBD=inflammatory bowel disease; IL=interleukin; IV=intravenous; N=number of participants; n=number of participants; RNA=ribonucleic acid; SE=standard error; UC=ulcerative colitis; WK=week.

Note: Combined guselkumab induction dose group (combined participants from the guselkumab 200 mg IV and 400 mg IV dose groups).

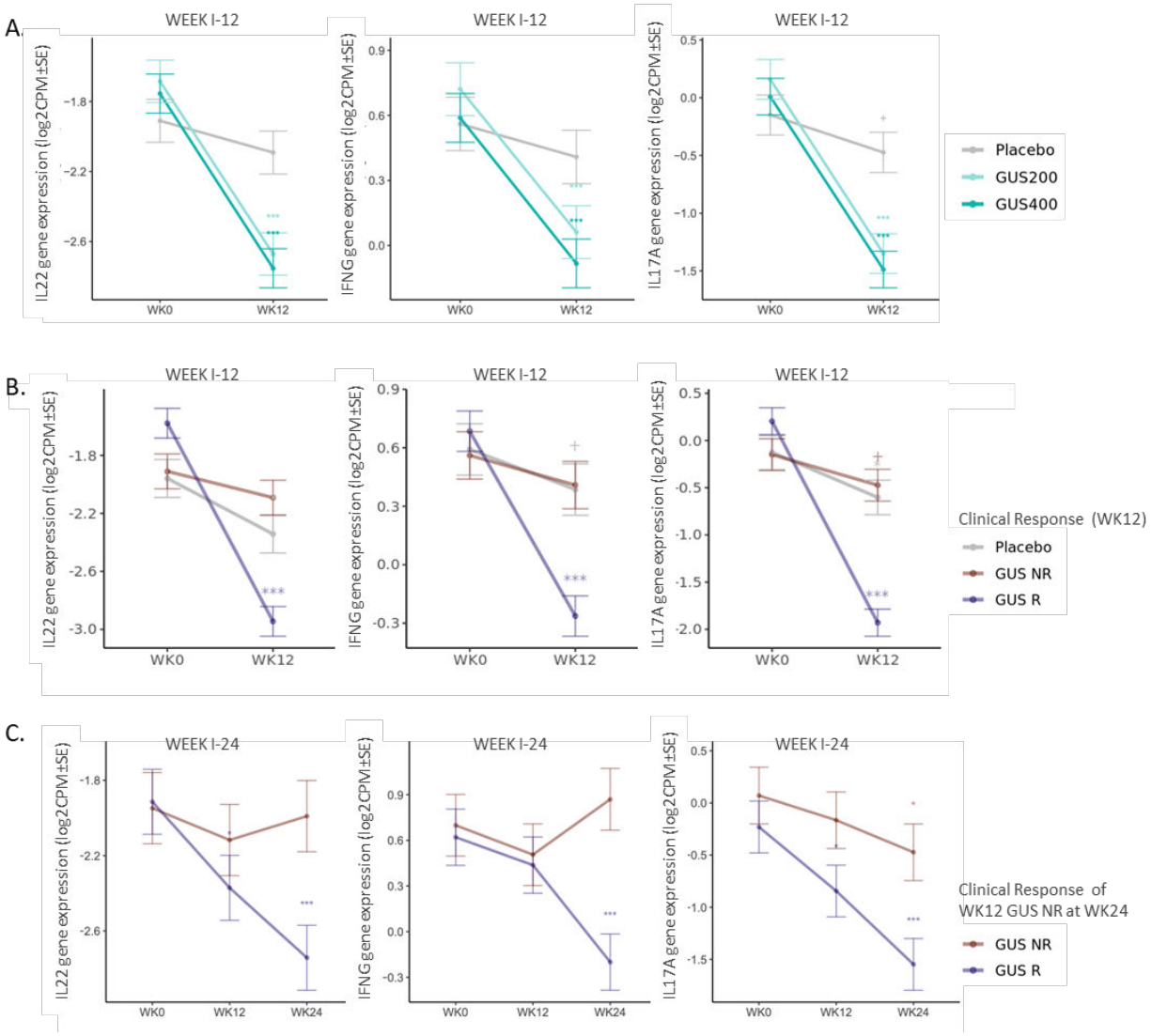
Note: Gene expression was measured with RNA sequencing as log2CPM in colon tissue. A. Gene expression of IL-23p19 (IL23A) in UC colon tissue at baseline (n=176) relative to guselkumab treatment (UC WK12) (N=176) and non-IBD Control (n=12).

p-Values: **** <0.0001, *** <0.001.

Significant reduction in the mRNA expression levels of IL-23-dependent pharmacodynamic biomarkers IL-22, IL-17A and IFNγ in colon tissue with both doses of guselkumab (GUS 200mg and 400mg) demonstrating the direct impact of IL-23p19 antagonism by guselkumab in colon tissue. Patients treated with guselkumab for 12 weeks showed a significant reduction in the expression of IL-22 (logFC=-1.25, adjusted P=3.89E-16), IFNγ(logFC=-0.58, adjusted P=7.52E-09), and IL-17A (logFC=-1.47, adjusted P=3.75E-16).

Gene expression levels of IL-23 dependent biomarkers IL-22, IFNγ, and IL-17A evaluated in colon tissue pre- and post-guselkumab treatment are presented in Figure 7.

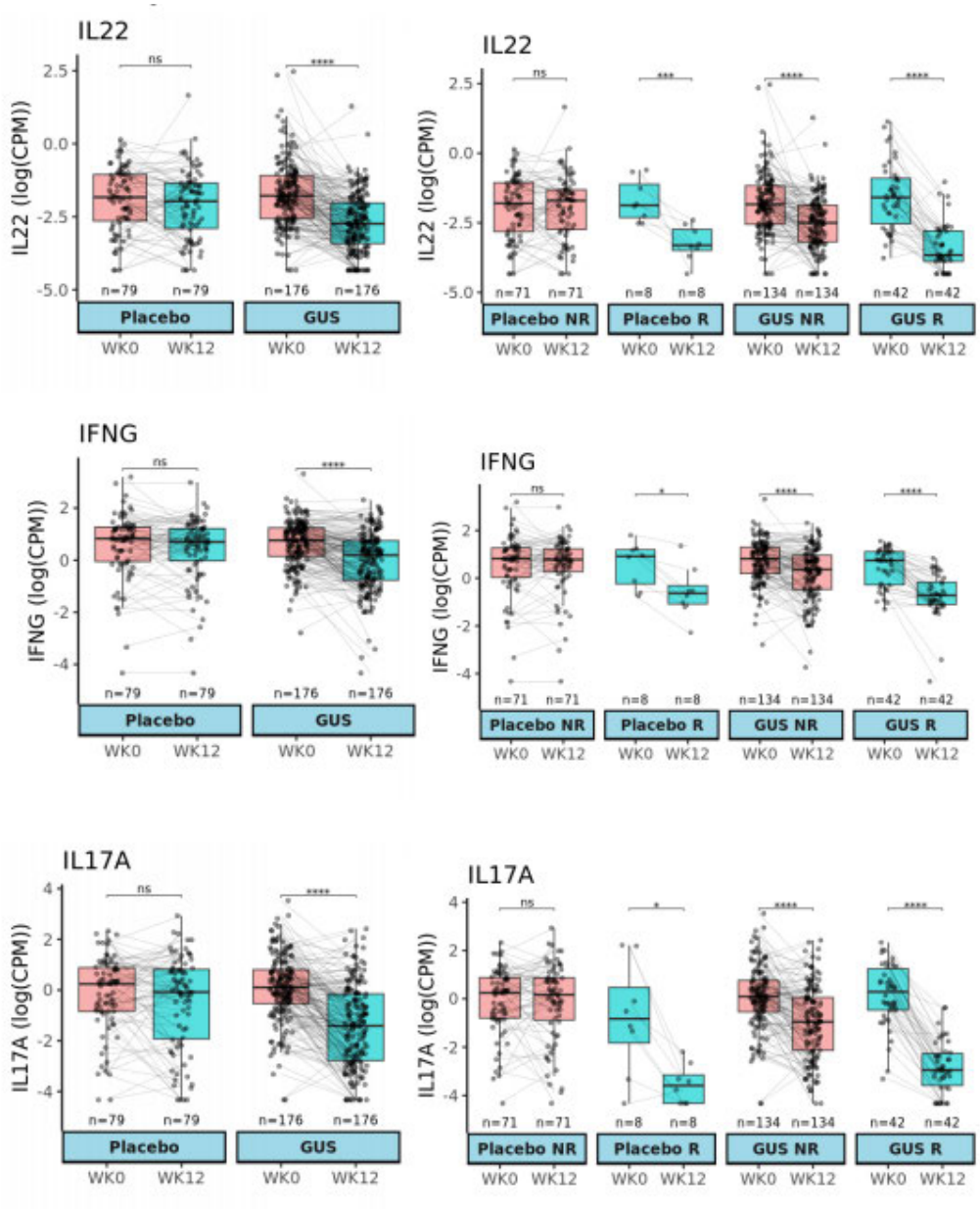
**Figure 7: Tissue Gene Expression Changes in IL-23-dependent Biomarkers IL-22, IFNγ, and IL-17A at Week I-12 and Week I-24; Randomized Analysis Set (Study CNTO1959UCO3001; Induction Study 1)**




Abbreviations: CPM=counts per million; GUS=guselkumab; GUS200=guselkumab 200 mg IV; GUS400=guselkumab 400 mg IV; I=induction; IFNγ/IFNG=interferon gamma; IL=interleukin; IV=intravenous; n=number of participants; NR= clinical nonresponders; R=clinical responders; RNA=ribonucleic acid; SE=standard error; WK=week.
Note: Combined guselkumab induction dose group (combined participants from the guselkumab 200 mg IV and 400 mg IV dose groups).
Note: Gene expression was measured with RNA sequencing as log2CPM in colon tissue.
A. Gene expression changes in placebo (n=79) and guselkumab 200 mg IV (n=81) and 400 mg IV (n=95) induction dose groups at Week 12 (WK12) compared with baseline (WK0).
B. Gene expression changes in combined guselkumab induction dose group stratified by clinical response status at Week 12 (WK12) relative to placebo.
C. Gene expression changes in Week 12 nonresponders (WK12 GUS NR) that received additional guselkumab induction dosing up to Week 24 (WK24), stratified by clinical response status at the end of the additional induction dosing period (WK24).
Nominal p-values: *** <0.001, ** <0.01, * <0.05.

Stratification of patients by their HEMI (histoendoscopic mucosal improvement) response status at Week 12 allowed for correlation of relevant tissue-based clinical efficacy outcomes with the molecular outcome of the treatment effect of guselkumab (combined dose) on the expression of key IL-23 dependent PD markers (Figure 8).

**Figure 8: Treatment effect on key PD marker genes, stratified by HEMI (Histo Endo Mucosal Healing) response.**



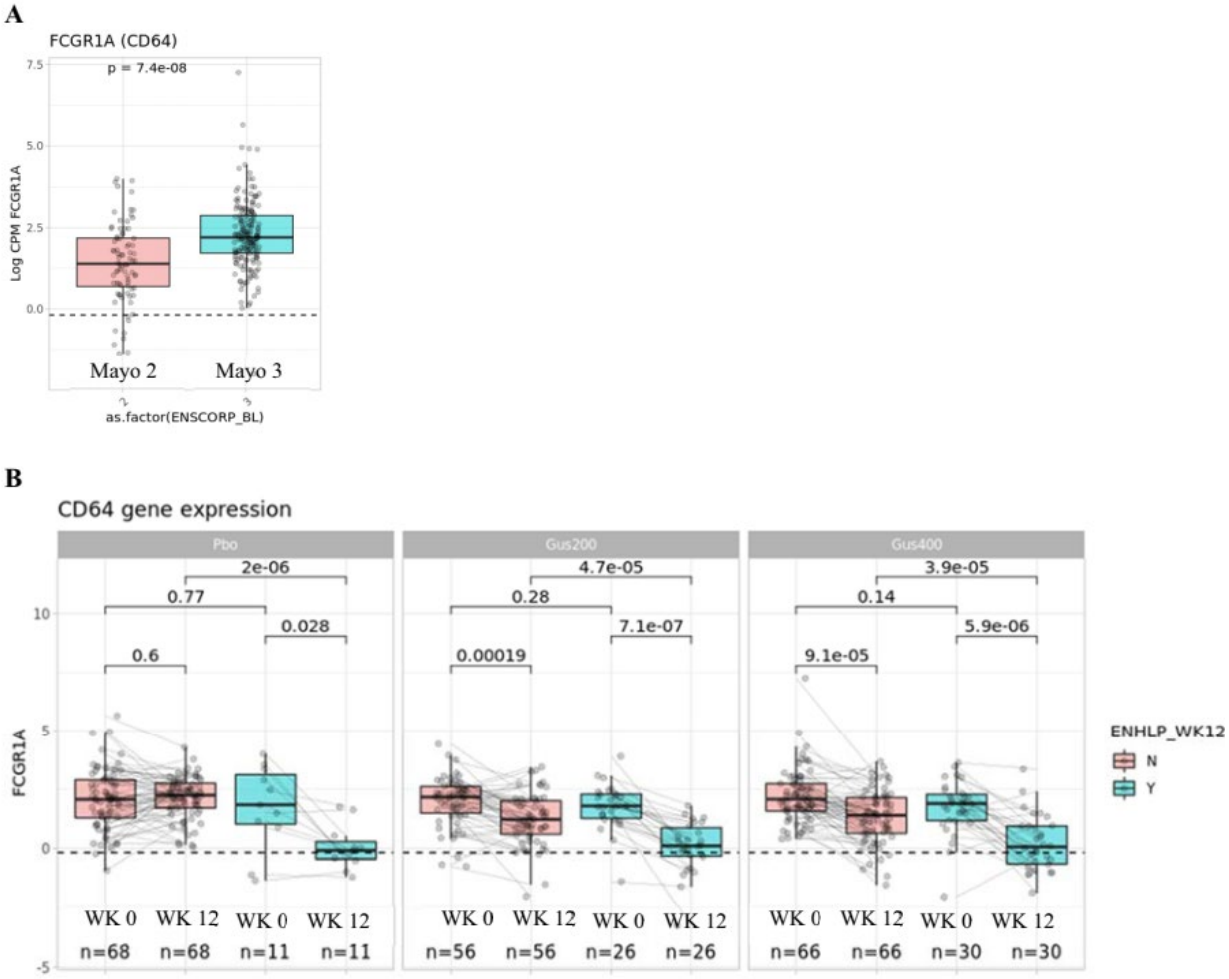

CPM=counts per million; IFNγ/IFNG=interferon gamma; IL=interleukin; WK=week; R=responder; NR= non-responder ; n= number of patients analyzed

Change in RNAseq Counts Per Million (CPM) in colon tissue at Week 12 compared with baseline. Data represent combined guselkumab 200mg and 400mg IV dose groups and placebo.

P values: *** < 0.001, ** < 0.01, * < 0.05

Transcriptomics studies proved the importance of the CD64 molecule in pathology and the effect of treatment on CD64 expression.

**Figure 9: CD64 tissue gene expression is increased with increasing disease severity (Mayo Endoscopy score2 vs 3, panel A) and decreased with treatment and shows larger decreases in patients demonstrating endoscopic healing at week 12 (panel B).**




CPM=counts per million; FCGR1A= Fc gamma receptor Ia; Mayo 2 & 3 = endoscopy mayo score; ENHLP=Endoscopic response; WK=week; Y=responder; N= non-responder; n= number of patients analyzed Change in RNAseq Counts Per Million (CPM) in colon tissue at Week 12 compared with baseline. Data represent combined guselkumab 200mg and 400mg IV dose groups and placebo. P values: *** < 0.001, ** < 0.01, * < 0.05

**Serum Proteomics**

Serum IL-22, IL-17A, and IFNγ were significantly decreased significantly following guselkumab induction treatment but not placebo.

In contrast to tissue transcriptomic results, reductions in IFN-gamma levels were independent of endoscopic response. There was no statistically significant difference in key plasma biomarkers between advanced therapy failure (ADT failure) and bio-naive populations. At the end of the induction period, the markers decreased almost to the same extent as a result of guselkumab treatment.

**Immunogenicity**

Using drug-tolerant ADA and NAb assays, the incidence of ADAs and NAbs to guselkumab was low through QUASAR Induction and Maintenance Studies in participants with UC.

Among 614 participants in the guselkumab 200 mg IV and 400 mg IV groups with appropriate samples in IS-1 and IS-2, 6 (1.0%) were positive for antibodies to guselkumab through Week I-12. None of the 6 participants were positive for NAbs.

Of the 508 participants who received guselkumab 200 mg IV induction with appropriate samples in IS-1 and IS-2, 6 (1.2%) were positive for antibodies to guselkumab through Week I-12. None of these 6 participants were positive for NAbs.

Of the 409 participants in the guselkumab 200 mg IV group with appropriate samples in IS-2, 6 (1.5%) participants were positive for antibodies to guselkumab through Week I-12. None of the 6 participants were positive for NAbs.

Among the 690 treated participants with appropriate samples for antibodies (ie, randomized placebo and guselkumab treatment groups and guselkumab Week I-24 responders) in the Maintenance Study, 72 (10.4%) participants were positive for antibodies to guselkumab through Week M-44. Of the 72 participants who were positive for antibodies to guselkumab, the majority (55/72, 76.4%) had a peak titer of 1:11.25, which was the minimum required dilution for the ADA detection assay. The overall incidence of NAbs among participants who received guselkumab and had appropriate samples was 1.4% through Week M-44.

Of the 501 participants who received continuous guselkumab treatment (ie, the randomized guselkumab treatment groups and the guselkumab Week I-24 responders) and had appropriate samples for antibodies in the Maintenance Study, 58 (11.6%) were positive for antibodies to guselkumab through Week M-44. Most (42/58, 72.4%) of the ADA-positive participants had a peak titer of 1:11.25. The overall incidence of NAbs among participants who received continuous guselkumab treatment was 1.8% through Week M-44.

Concomitant use of immunomodulators (ie, AZA, 6-MP, MTX) did not have an apparent impact on the development of antibodies to guselkumab. Among the participants who received IV induction of 200 mg q4w and SC maintenance of 200 mg q4w and 100 mg q8w, the incidences of antibodies to guselkumab through Week M-44 in the presence of immunomodulator use was 12.1% compared with 10.8% in participants not receiving immunomodulators.

Among participants with and without baseline immunomodulator use, the incidences of antibodies to guselkumab through Week M-44 were 12.1% and 10.8%, respectively. Overall, no apparent impact of the concomitant immunomodulator use on the development of antibodies to guselkumab was observed.

**Effect of Immunogenicity on Efficacy**

**Induction**

The effect of ADA status (positive or negative) on selected efficacy endpoints at Week I-12 was evaluated in randomized participants in IS-2. Of the 409 participants in the guselkumab 200 mg IV group with appropriate samples in IS-2, the incidence of antibodies to guselkumab through Week I-12 was 6/409, 1.5%, and no participant developed NAbs to guselkumab in IS-2. No relationship was observed between the key efficacy endpoints at Week I-12 and the antibodies to guselkumab status through Week I-12.

**Maintenance**

The effect of ADA status on selected efficacy endpoints was evaluated in pooled data from 334 participants in the Maintenance Study who received the Phase 3 guselkumab dose regimens (ie, 200 mg IV q4w for induction; 100 mg SC q8w or 200 mg SC q4w for maintenance treatment). The development of antibodies to guselkumab in general did not have an apparent impact on clinical efficacy as measured by multiple endpoints such as clinical remission, clinical response, endoscopic healing at Week M-44. Among the 32 participants who were positive for antibodies to guselkumab through Week M-44 in the combined dose group (100 mg SC q8w and 200 mg SC q4w), 14 participants (43.8%) achieved clinical remission, 24 (75.0%) achieved clinical response, and 15 (46.9%) achieved endoscopic healing at Week M-44. Among the 302 participants in the combined dose group who were negative for antibodies to guselkumab through Week M-44, 142 (47.0%) participants achieved clinical remission, 229 (75.8%) achieved clinical response, and 151 (50.0%) achieved endoscopic healing at Week M-44.

**Effect of Immunogenicity on Safety**

Through induction studies, the effect of antibody status on the proportion of participants who experienced an AE within 1 hour of infusion was assessed in pooled data from randomized participants who received 200 mg IV induction treatment through Week I-12.

The development of antibodies to guselkumab did not have an apparent impact on AE incidence within 1 hour of infusion through Week I-12. None of the 6 participants who were positive for antibodies to guselkumab through Week I-12 reported an AE within 1 hour of receiving a guselkumab infusion. Eight (1.6%) of the participants who were negative for antibodies to guselkumab through Week I-12 reported an AE within 1 hour of receiving a guselkumab infusion.

The development of antibodies to guselkumab did not have an apparent impact on AEs within 1 hour of infusion (IS-1 and IS-2) or injection-site reactions (Maintenance Study).

**Comparison of Immunogenicity between Participants with UC and Participants with CD**

Immunogenicity results for participants with UC are presented for participants who received continuous guselkumab treatment in QUASAR, ie, participants who received IV guselkumab induction and then were randomized to one of the guselkumab treatment groups, as opposed to the placebo group. Comparisons of the incidence of antibodies between participants with UC and CD were performed at identical timepoints.

Through Week 12, following induction treatment with guselkumab 200 mg IV q4w, the incidence of antibodies to guselkumab was similarly low between participants with UC (1.2%, [6 of 508 participants]) and participants with CD in the combined GALAXI studies (1.3%, [8 of 634 participants]).

After 48 weeks with the same induction (200 mg IV q4w) and maintenance regimen (100 mg SC q8w or 200 mg SC q4w), there was a l difference in the incidence of antibodies to guselkumab in

participants with UC compared with participants with CD. The incidence of antibodies to guselkumab was 8.1% (27 of 334 participants) in participants with UC and 4.7% (29 of 616 participants) in participants with CD (in both maintenance guselkumab treatment groups). Overall, the incidence of antibodies across UC and CD was 5.9% (56 of 950 participants) through Week 48.

**PK/PD modelling**

Four selected key efficacy endpoints, clinical remission and endoscopic healing were used as representative endpoints for presenting E-R results for both Induction and Maintenance Studies. The definition of these endpoints are given in Table 10.

**Table 10: Key Efficacy Endpoints at Week M-44 Evaluated in the E-R Analyses for Efficacy**

| Efficacy endpoints | Definition |
|---|---|
| Clinical remission | Mayo stool frequency subscore of 0 or 1 where the stool frequency subscore has not increased from induction baseline, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1, with no friability present on the endoscopy, |
| Clinical response | Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.<br>Modified Mayo score: 3-component (stool frequency, rectal bleeding, and endoscopy subscores), ie, Mayo score without the physician's global assessment. |
| Endoscopic healing (ie, improvement in the endoscopic appearance of the mucosa) | Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy |
| Histologic-endoscopic mucosal healing | Achieving a combination of histologic healing and endoscopic healing:<br>• Histologic healing: neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system |

Abbreviations; E-R=exposure-response; Week M-44=maintenance week 44.

**E-R Analyses for Induction Efficacy**

Initial exploratory E-R analysis suggested apparent positive E-R relationships between systemic guselkumab exposures ($C_{trough,week12}$ and $C_{ave,week0-12}$) and efficacy endpoints at Week I-12, ie, clinical remission, clinical response, endoscopic healing, and histologic-endoscopic mucosal healing. No dose response was observed across all these efficacy endpoints when comparing clinical results across the 2-fold dose range (200 vs 400 mg IV q4w), suggesting that a confounding factor may be present. It was hypothesized that the disposition characteristics ($T_{1/2}$ or CL) instead of the level of exposure to guselkumab could be associated with the response of individual participants to the treatment. The mechanisms by which $T_{1/2}$ or CL affect the guselkumab response are unknown; however, this finding suggests that $T_{1/2}$ and CL of guselkumab may be related to the underlying disease for individual

patients, and their treatment effect may not be further improved by dose increases once the guselkumab exposure is sufficiently high for efficacy. A similar finding was reported for vedolizumab, an anti-α4β7 integrin mAb for the treatment of UC and CD, where high drug clearance was associated with lower efficacy and dose optimization based on drug exposure failed to show clinical efficacy benefit as compared with the standard therapy (ie, continuing to use the recommended dosage) (Osterman 2019[38], Jairath 2023[39]).

Further E-R analyses were conducted, which revealed that participants with longer $T_{1/2}$ (slower CL) in both IS-1 and IS-2 responded better to guselkumab relative to participants with shorter $T_{1/2}$ (faster CL), regardless of the induction dose groups of 200 mg and 400 mg IV. After accounting for individual guselkumab CL or $T_{1/2}$, no apparent E-R relationships remained for any of the tested efficacy endpoints. These findings are consistent with the observed lack of dose response of guselkumab during IV induction in participants with UC in IS-1, supporting the use of 200 mg IV q4w for induction.

**Efficacy Analyses for Maintenance Efficacy**

Similar to induction, initial exploratory E-R analyses also suggested positive E-R relationships between steady-state guselkumab exposures ($C_{trough,week44}$ and $C_{ave,week36-44}$) and efficacy endpoints at Week M-44 (ie, clinical remission, clinical response, endoscopic healing, and histologic-endoscopic mucosal healing) following maintenance treatment with guselkumab. The E-R relationships were consistent with the observed clinical efficacy results from the QUASAR Maintenance Study, where the 200 mg SC q4w dose regimen showed numerically higher proportions of participants achieving certain key efficacy endpoints in the primary analysis population, including clinical remission (primary endpoint), histologic-endoscopic mucosal healing, and maintenance of clinical remission relative to the 100 mg SC q8w dose regimen.

**E-R modelling of Maintenance Efficacy**

Based on AIC criteria comparing logistic model fittings using linear, log-linear, or Emax functions, the Emax model was selected as the best function to describe E-R relationships between exposure metrics:

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

Ctrough at week 44 was selected as the best predictor for efficacy in subsequent E-R logistic regression model development.

As the base E-R models were selected to be the nonlinear sigmoid Emax model, covariate searches were performed on the intercept (efficacy response in the absence of drug exposure), EC50, and Emax. For continuous covariates, the potential effects were tested additively on the intercept in the logit scale or multiplicatively on EC50 and Emax as power models. Additionally, 2 continuous covariates, CRP and CALP levels at induction and maintenance baseline, were dichotomized at given cutoff values of clinical interest and subsequently treated as categorical covariates.

The final E-R model indicates that the extent of disease was an influential factor on the Emax parameter for clinical remission at Week M-44. Specifically, participants with extensive disease status tend to have more room for potential increase in the probability of achieving clinical remission compared with participants with limited disease status. Therefore, higher guselkumab exposure would result in larger benefit, in terms of clinical remission at Week M-44, in the subpopulation with extensive disease at induction baseline. Moreover, the model suggests that participants who are in

[38] Osterman MT, Rosario M, Lasch K, et al. Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. Aliment Pharmacol Ther. 2019;49(4):408-418.
[39] Jairath V, Yarur A, Osterman MT, et al. ENTERPRET: A Randomized controlled trial of vedolizumab dose optimization in patients with ulcerative colitis who have early nonresponse. Clin Gastroenterol Hepatol. 2023:S1542-3565(23)00912-6.

clinical remission at maintenance baseline tend to have a higher probability of achieving clinical remission at Week M-44 due to a higher intercept (ie, probability of response in the absence of drug exposure) of the E-R curve. On the other hand, clinical remission status at maintenance baseline does not affect the increase in response rate caused by the increased guselkumab exposure. The distribution of the Ctrough, week44 concentrations across the E-R curve also suggests that while the 200 mg q4w regimen may more effectively cover the upper portion of the E-R curve associated with the highest clinical remission rates at Week M-44, the 100 mg SC q8w regimen may also be effective for certain participants, especially those already in clinical remission following induction treatment. Therefore, no evidence of benefit from a higher guselkumab exposure was identified in the subpopulation that was already in clinical remission at the time of maintenance randomization.

Covariate analysis for the E-R relationships demonstrated that the extent of UC disease (based on screening endoscopy or medical history) was an influential factor on the $E_{max}$ across all 4 selected key efficacy endpoints at Week M-44 (ie, clinical remission, clinical response, endoscopic healing, and histologic-endoscopic mucosal healing), indicating that for a given concentration, participants with extensive UC disease exhibit a greater magnitude of treatment effect. Model-predicted E-R relationships stratified by relevant covariates for the endpoints of clinical remission and endoscopic healing are shown in Figure 10 and Figure 11, respectively.

**Figure 10: Model-predicted E-R Relationships for Clinical Remission Using $C_{trough,week44}$ as the PK Exposure Metric in Participants With UC, Stratified by the Extent of UC Disease at induction Baseline (Right) and Stratified by Clinical Remission Status at Maintenance Baseline (Left)**

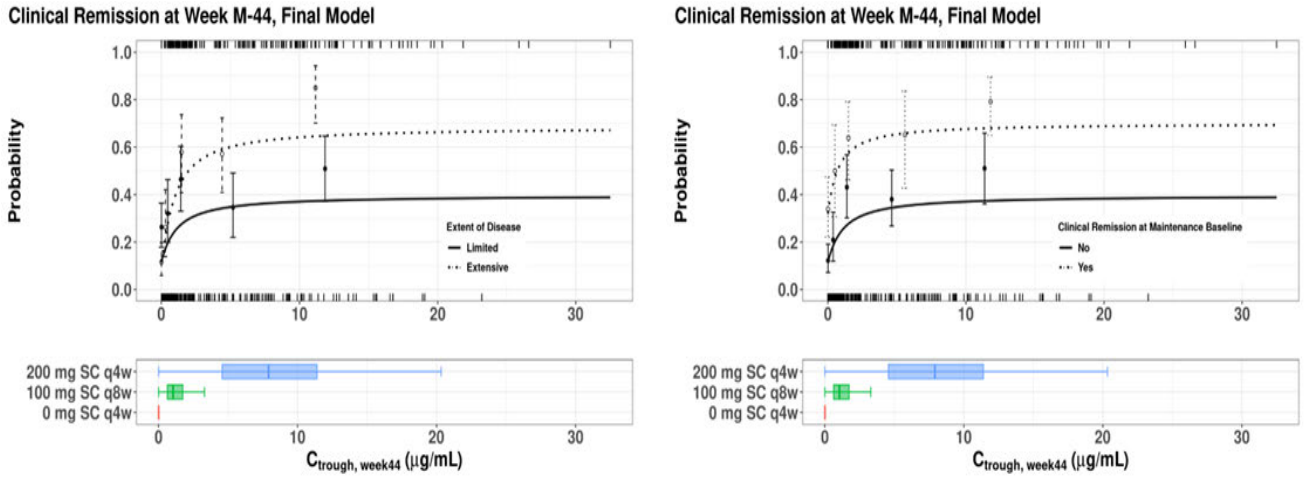
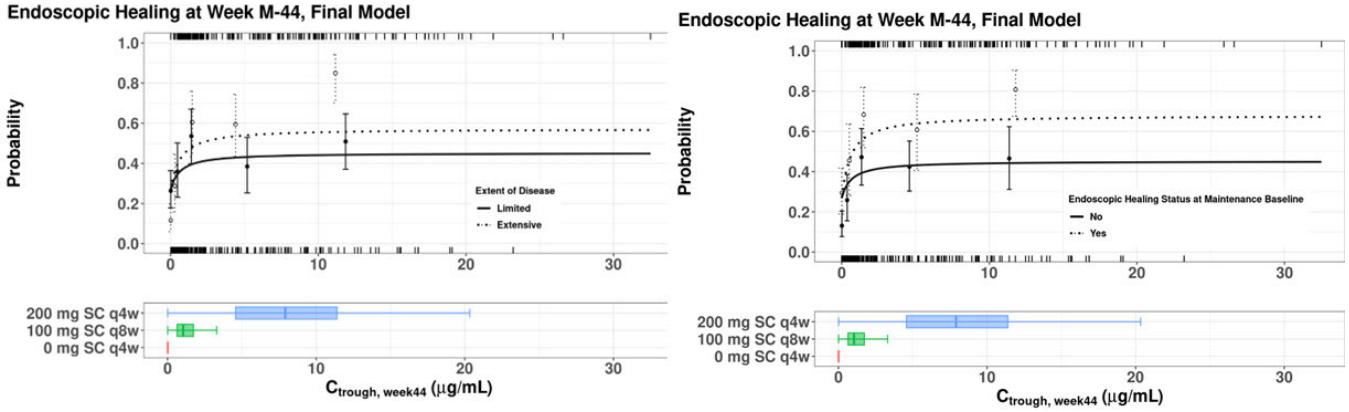


**Figure 11: Model-predicted E-R Relationships for Endoscopic Healing Using $C_{trough,week44}$ as the PK Exposure Metric in Participants With UC, Stratified by the Extent of UC Disease at Induction Baseline (Left) and Stratified by Endoscopic Healing Status at Maintenance Baseline (Right)**




Abbreviations: CI=confidence interval; $C_{trough}$=serum trough concentration; E-R=exposure-response; IQR=interquartile range; PK=pharmacokinetic; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; UC=ulcerative colitis; Week M-44=maintenance week 44.
Note: The curves represent model-predicted probabilities of achieving clinical remission at Week M-44 (dashed curve for participants with extensive UC disease at induction baseline and solid curve for participants with limited UC disease at induction baseline at the top panel, or dashed curve for participants in clinical remission at maintenance baseline and solid line for participants NOT in clinical remission at maintenance baseline at the bottom panel). The symbols with error bars represent the observed rate (median with 95% CI) of clinical remission in each exposure quartile bin stratified by extent of UC disease at induction baseline (open circles for extensive UC disease at induction baseline and closed circles for limited UC disease at induction baseline at the top panel), or clinical remission status at maintenance baseline (open circles for clinical remission at maintenance baseline and closed circles for NOT in clinical remission at maintenance baseline at the bottom panel). The box plots at the bottom of the charts represent the distribution of model-predicted steady-state $C_{trough}$ for each of the 2 maintenance dose regimens of 100 mg SC q8w and 200 mg SC q4w at Week M-44 ($C_{trough,week44}$): the center line of the box is the median Ctr_W44; the left and right ends of the box are the 25th and 75th percentiles of $C_{trough,week44}$, respectively, and the box represents the IQR of $C_{trough,week44}$; the left and right whiskers of the box cover the bounds of 1.5×IQR of $C_{trough,week44}$. The smooth curves represent the model-predicted E-R relationships for subgroups stratified by a given covariate (the extent of UC disease at induction baseline at the top panel, or clinical remission at maintenance baseline at the bottom panel) while other covariates were fixed to be the same as the reference group in the final model. In contrast, the symbols with error bars represent the observed efficacy rates for each of the $C_{trough,week44}$ quartiles stratified by 1 associated covariate, which could be confounded by the effects from other covariates as they were not fixed as in the reference group. The reference group in the final model for clinical remission at Week M-44 was participants who did not achieve remission at maintenance baseline, and who had limited UC disease at induction baseline.

Model-predicted response rates for these 2 endpoints at 100 mg SC q8w and 200 mg SC q4w regimens stratified by relevant covariates are also compared numerically (Table 11 and Table 12). Results for clinical response and histologic-endoscopic mucosal healing indicate that higher guselkumab exposure is expected to result in a greater probability of achieving all 4 efficacy endpoints in the overall population and particularly those with extensive UC disease at induction baseline.

**Table 11: Clinical Remission at Week M-44, Response Rate Summary by Extent of Disease; E-R Analysis Set (Study CNTO1959UCO3001; Maintenance Study)**

| Regimen | Extent of Disease | Observed Response Rate (%) | Simulation Median (95% CI) (%) |
|---|---|---|---|
| 100 mg SC q8w | Limited | 42.2 | 36.15 (25.51, 48.63) |
| 100 mg SC q8w | Extensive | 49.37 | 48.33 (34.52, 64.01) |
| 200 mg SC q4w | Limited | 40.19 | 47.47 (35.13, 59.23) |
| 200 mg SC q4w | Extensive | 62.65 | 68.24 (53.26, 81.92) |

Abbreviations: CI=confidence interval; E-R=exposure-response; M=maintenance; q4w=once every 4 weeks; q8w=once every 8 weeks; SC=subcutaneous.

**Table 12: Endoscopic Healing at Week M-44, Response Rate Summary by Extent of Disease; E-R Analysis Set (Study CNTO1959UCO3001; Maintenance Study)**

| Regimen | Extent of Disease | Observed Response Rate (%) | Simulation Median (95% CI) (%) |
|---|---|---|---|
| 100 mg SC q8w | Limited | 47.71 | 39.11 (28.04, 51.46) |
| 100 mg SC q8w | Extensive | 51.9 | 50.57 (36.78, 64.29) |
| 200 mg SC q4w | Limited | 42.06 | 49.51 (36.56, 62.11) |
| 200 mg SC q4w | Extensive | 63.86 | 66.67 (50.56, 79.44) |

Abbreviations: CI=confidence interval; E-R=exposure-response; M=maintenance; q4w=once every 4 weeks; q8W=once every 8 weeks; SC=subcutaneous.

Some additional covariates were found to be associated with the probability of achieving efficacy endpoints at Week M-44; however, no substantial differences in efficacy response rates were identified in subpopulations stratified by these covariates for the 4 efficacy endpoints. Moreover, the trend for these covariates was not consistent across endpoints. The covariates that were retained in the final models for each efficacy endpoint at Week M-44 are listed in Table 13.

**Table 13: Covariates Selected for Efficacy Endpoints in the Week M-44 Exposure Landmark Analysis**

| | Clinical Remission | Clinical Response | Endoscopic Healing | Histologic-endoscopic Mucosal Healing |
|---|---|---|---|---|
| Extent of disease[a] | $E_{max}$ | $E_{max}$ | $E_{max}$ | $E_{max}$ |
| Clinical remission status at maintenance baseline | Intercept | | | Intercept |
| Endoscopic healing status at maintenance baseline | | | $E_{max}$ | |
| Corticosteroid use[a] | | Intercept | | |
| ADT failure status | | Intercept | | |
| Albumin[a] | | | | Intercept, $EC_{50}$ |
| Fecal calprotectin at maintenance baseline | | | Intercept, $E_{max}$ | Intercept, $EC_{50}$ |

Abbreviations: ADT=advanced therapy; $EC_{50}$=exposure metric level corresponding to 50% of the maximum drug effect; $E_{max}$=maximum drug effect; Week M-44=maintenance week 44.

Note: Intercept, EC50, or $E_{max}$ represent a model parameter to which a covariate was added as a significant factor.

[a] Induction baseline characteristic.

*Target threshold model*

The analysis included all E-R evaluable data at Week I-12 (a total of 1,013 participants evaluable for E-R analysis in the induction phase, as described in the PopPK and E-R report in the initial UC submission). The exposure metric was the PopPK model-predicted individual guselkumab concentration value ($C_{trough, week12}$), based on the actual dosing records for each participant. Potential optimal concentration thresholds associated with clinical remission at Week I-12 and endoscopic healing at Week I-12 were determined using ROC curve analysis, based on the Youden index.

The summary of ROC curve analysis is shown in Table 15. Median $C_{trough, week12}$ of the 200 mg IV q4w treatment group (8.42 µg/mL) is above the estimated threshold concentrations of clinical remission (6.56 µg/mL) and endoscopic healing (6.85 µg/mL) at Week I-12, therefore a majority of participants were above these thresholds. ROC curves for both efficacy endpoints at Week I-12 are presented in Table 14. The AUROC, a performance metric summarizing the model performance, is 70.1% for clinical remission and 69.0% for endoscopic healing at Week I-12. An AUROC of approximately 70% suggests some predictive power, but the presence of unknown latent factors likely affects the threshold from the ROC analysis. Although the ROC results support that 200 mg IV q4w is an efficacious induction regimen, these threshold levels identified by the ROC analyses should be interpreted with caution since a higher dosage (400 mg IV q4w versus 200 mg IV q4w) was not shown to increase clinical efficacy in the QUASAR Phase 2b Induction Study.

Given that the efficacy was similar across the primary endpoint and major secondary endpoints between 200 mg IV q4w and 400 mg IV q4w in QUASAR, the Applicant selected the lower IV induction dose regimen of 200 mg q4w for confirmatory evaluation in the QUASAR Phase 3 induction study (Induction Study 2).

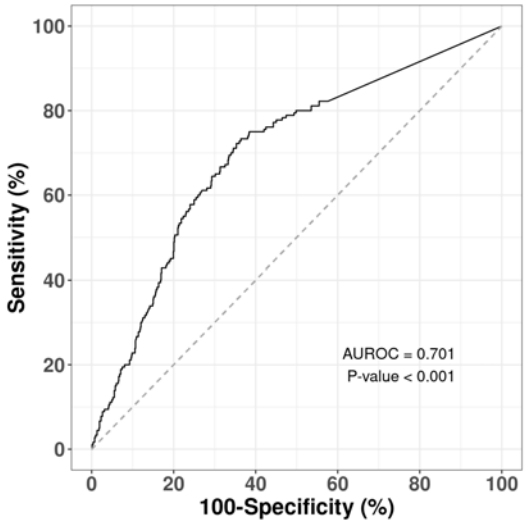
**Table 14: ROC Curve Analysis Metrics for the Relationship Between Guselkumab Trough Concentration at Week I-12 and Efficacy at Week I-12; E-R Analysis Set (Study CNTO1959UCO3001; Induction Studies 1 and 2)**

| Efficacy Outcome at Week I-12 | ROC Curve Metrics | Analysis Findings |
|---|---|---|
| Clinical Remission | AUROC (95% CI; p-value) | 70.1% (65.95%, 74.31%; p < 0.001) |
| | Sensitivity/Specificity/PPV/NPV, % | 73.3/63.6/30.3/91.7 |
| | Threshold [a], µg/mL | 6.56 |
| | Proportion of 200 mg IV recipients having $C_{trough,\ week12}$ above threshold, % | 64.5 |
| Endoscopic Healing | AUROC (95% CI; p-value) | 69.0% (65.04%, 72.93%; p < 0.001) |
| | Sensitivity/Specificity/PPV/NPV, % | 69.7/65.9/36.3/88.6 |
| | Threshold[a], µg/mL | 6.85 |
| | Proportion of 200 mg IV recipients having $C_{trough,\ week12}$ above threshold, % | 62.4 |

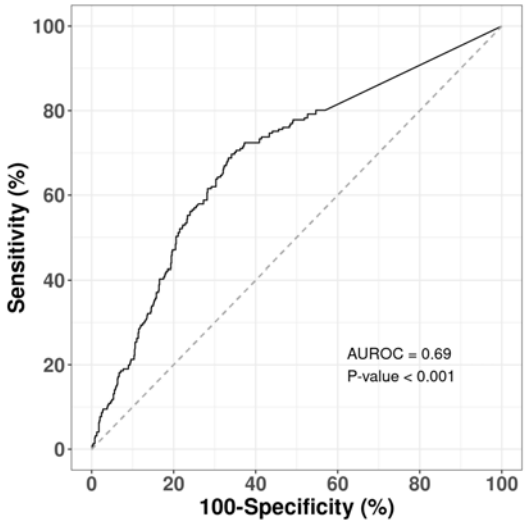
Abbreviations: AUROC=area under the receiver operating characteristic curve; CI=confidence interval;
Ctrough, week12=predicted guselkumab trough concentration at Week I-12 using population PK model; E-R=exposure-response; I=induction; IV=intravenous; NPV=negative predictive value; PK=pharmacokinetic; PPV=positive predictive value; ROC=receiver operating characteristic.
a Threshold=optimal cut-off values were chosen using the Youden index (Youden 1950), which maximizes the sum of the specificity and sensitivity of the ROC curve.

**Figure 12: ROC Curve Analysis of Guselkumab Trough Concentration at Week I-12 and Efficacy Outcomes at Week I-12 in the Induction Studies, Including (A) Clinical Remission, (B) Endoscopic Healing; E-R Analysis Set (Study CNTO1959UCO3001; Induction Studies 1 and 2)**

Clinical Remission




Endoscopic Healing

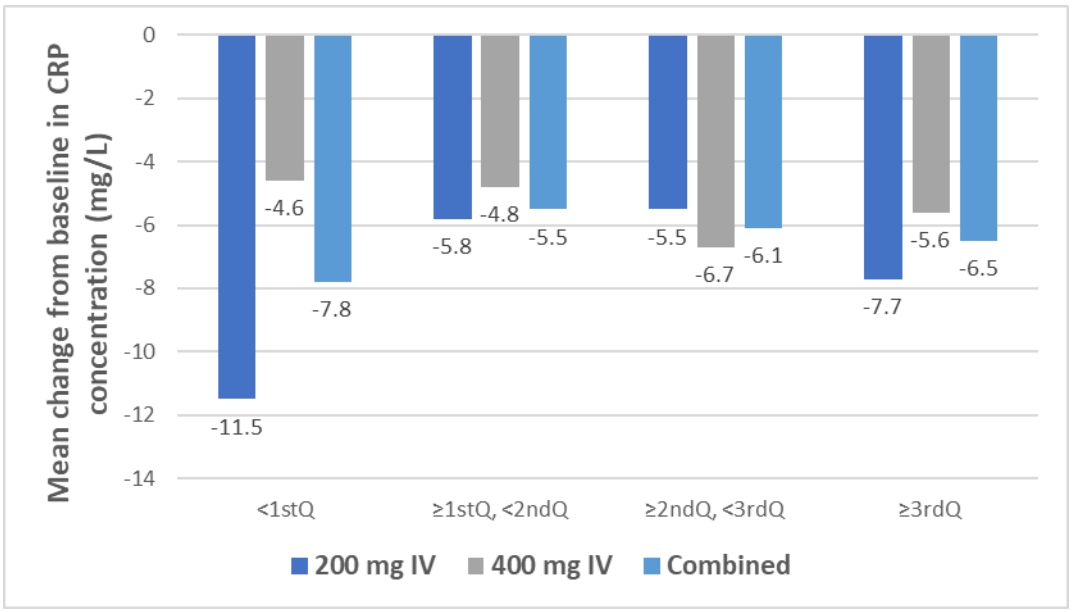



**E-R Analyses for biomarkers**

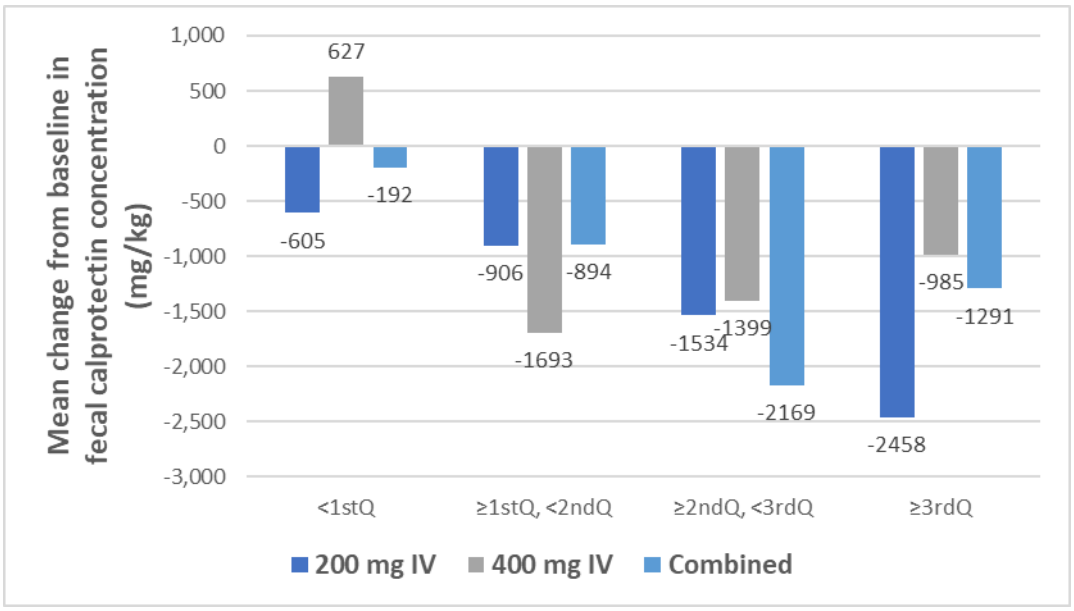
Following guselkumab 200 mg IV or 400 mg IV administration during induction, the concentration-effect relationship between guselkumab exposure and biomarker levels for the induction period evaluated using guselkumab Ctrough at Week I-12 and change from baseline in inflammatory biomarkers (ie, CRP and fecal calprotectin, 2 well--established biomarkers in UC) at Week I-12 are presented in Figure 13.

**Figure 13: Concentration-effect Relationship Between Guselkumab Exposure and Biomarker Concentrations (CRP and Fecal Calprotectin), Randomized Analysis Set (Study CNTO1959UCO3001; Week I-12)**

A.



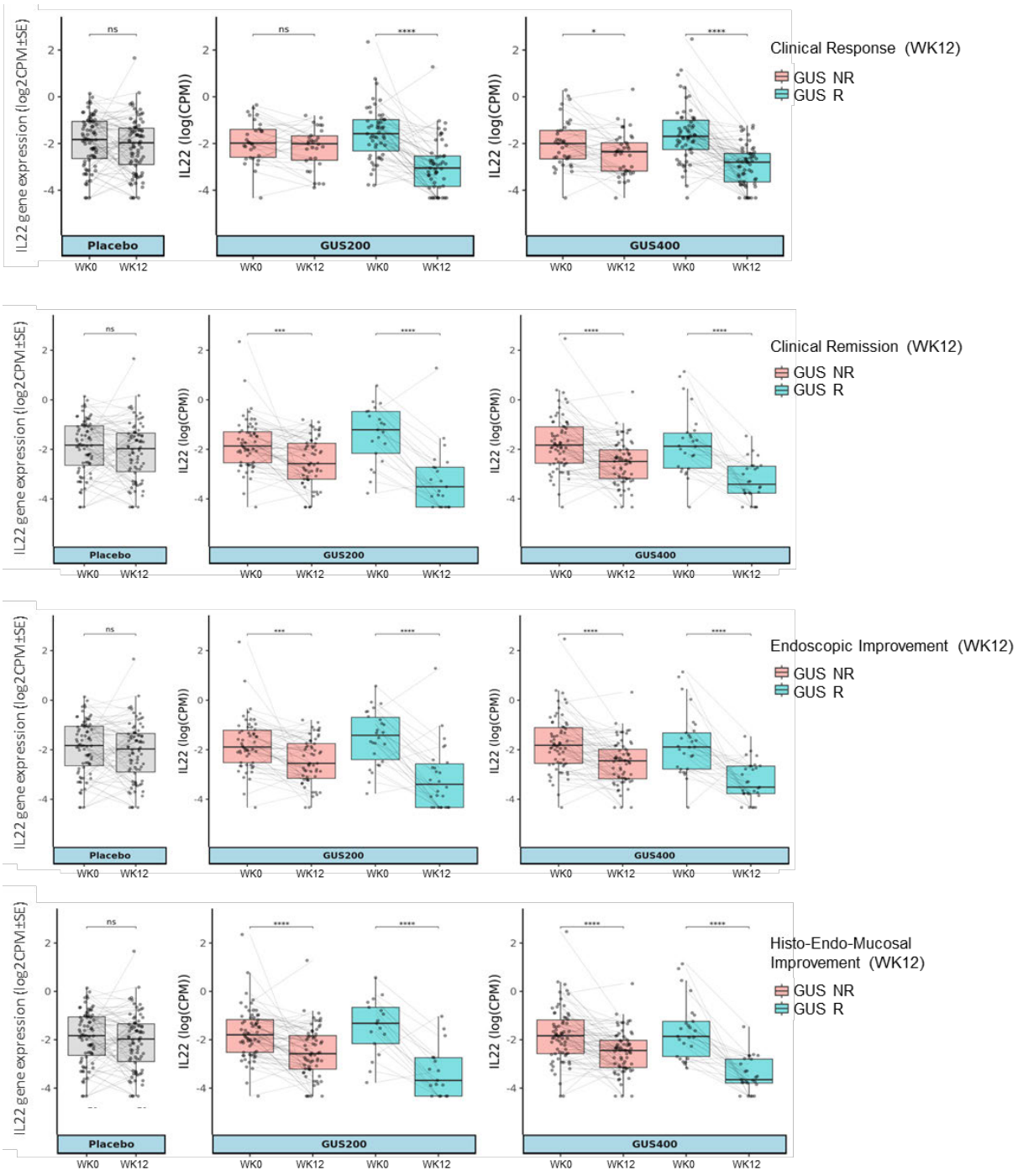

B.




Abbreviations: CRP=C-reactive protein; I=induction; IV=intravenous; Q=Quartile.

No dose-response was observed for the changes from baseline for IL-23 dependent biomarkers (IL-22, IL-17A, and IFNγ), therefore E-R analysis for these biomarkers is not considered meaningful. The Applicant has provided results from the evaluation of the relationship between the tissue gene expression changes in the IL-23-dependent biomarker IL-22 and key clinical endpoints at induction Week I-12 in the guselkumab 200 mg IV and 400 mg IV induction dose groups (Figure 14).

**Figure 14: Tissue Gene Expression Changes in IL-23-dependent Biomarker IL-22 Correlated to Clinical Efficacy Endpoints in the Guselkumab 200 mg IV and 400 mg IV Induction Dose Groups; Randomized Analysis Set (Study CNTO1959UCO3001; Induction Study 1)**




Abbreviations: CPM=counts per million; GUS=guselkumab; GUS200=guselkumab 200 mg IV; GUS400=guselkumab 400 mg IV; IFNγ/IFNG=interferon gamma; IL=interleukin; IV=intravenous; n=number of participants; NR= clinical nonresponders; R=clinical responders; RNA=ribonucleic acid; SE=standard error; WK=week.
Note: Gene expression was measured with RNA sequencing as log2CPM in colon tissue. Gene expression changes in placebo (n=79) and guselkumab 200 mg IV (n=81) and 400 mg IV (n=95) induction dose groups at Week 12 (WK12) compared with baseline stratified by response status for 4 efficacy endpoints: Clinical Response, Clinical Remission, Endoscopic Improvement and Histologic-Endoscopic-Mucosal-Improvement (Histo-Endo-Mucosal-Improvement).
Nominal p-values: *** <0.001, ** <0.01, * <0.05, ns; not significant

**E-R Analyses for Safety**

There was no association between average $C_{trough}$ and the selected safety events (infections, serious infections, and SAEs) and liver function tests (ALT, AST, total bilirubin) neither in the induction nor in the maintenance period.

## 2.6.3. Discussion on clinical pharmacology

In order to support this application, the MAH provided additional bioanalytical reports, 2 bioequivalence studies (studies CNTO1959EDI1001 and CNTO1959CRD1003), pharmacokinetic and pharmacodynamic parts of the pivotal phase 2b/3 QUASAR clinical report (CNTO1959UCO3001), a biomarker report related to the QUASAR study and a population PK and PK/PD report in UC patients using data obtained in Study QUASAR.

***Bioanalytics***

The assay to quantify guselkumab in plasma is essentially the same method that was used previously in the psoriasis clinical development programme. There are 11 minor changes related to the new patient population, additional stability testing, and the relocation of the analytical method from the US to a new testing site in China. Compared to the original assay, the method used to detect binding antibodies to guselkumab has been significantly improved. Guselkumab present in samples competes with ADA assay reagents, resulting in decreased assay sensitivity and potentially causing false negative results. The low tolerance limits were a source of concern during the previous submission. If not addressed, these low drug tolerance limits would have been issues in UC studies because the doses are higher, hence, leading to higher circulating guselkumab concentrations. To address the drug tolerance issue, the MAH improved the previous method, yielding markedly improved and acceptable drug tolerance limits. This is acceptable to the CHMP.

***Bioequivalence Study EDI1001***

In the QUASAR IS-1 and IS-2 studies, guselkumab for IV induction was supplied as a 100 mg/mL sterile liquid in 1 mL PFS-U (an approved SC presentation). The appropriate IV induction dose was prepared by transferring the contents of guselkumab 100 mg PFS devices into an IV bag containing 100 mL dextrose for infusion. To facilitate the IV induction administration of the selected 200 mg dose, a FVP (final vialed product) containing 200 mg, supplied in a 20 mL glass vial (i.e., 10 mg/mL), was developed as the to-be-marketed formulation and presentation for IV induction administration in participants with UC. It was not expected that there would be any change in the kinetics of guselkumab administered as an infusion (100 mL dextrose) depending on the guselkumab solution used for the preparation of the infusion. As expected, the study did not find any difference. This is acceptable to the CHMP.

***Bioequivalence Study CRD1003***

A bioequivalence study (CRD1003) was conducted in healthy participants to bridge the two new 2 mL SC injection devices (PFS-U and PFS-Y) with the approved 1 mL PFS-U presentation that was used to administer SC doses of guselkumab in Study QUASAR. Formally, the bioequivalence requirements between the 1 mL and 2 mL PFS-U devices were barely met: the confidence interval regarding the approved 100 mg formulation is 81.93 - 93.58. The 12.85% difference in the amount of absorbed guselkumab between the two injection devices containing the same solution is probably not significant therapeutically but identified as a cause for concern by the CHMP. The MAH's argument that the extent of absorption may depend on the injected volume is considered unlikely by the CHMP, as there was no such difference with the other tested device (2 mL PFS-Y). Two cases were reported in the study where the 2 mL PFS-U injection device was difficult to handle, while no such complaints arose with the other

two devices (1 mL PFS-U and 2 mL PFS-Y). Upon the CHMP's request, the MAH clarified that the 2.0 mL PFS-U devices were returned to the sponsor since its usage was felt different compared to the two other devices used in the study. Furthermore, the 2.0 mL of PFS-U was used successfully in an additional clinical study (Study GALAXI). Hence, the issue was not further pursued.

The CHMP raised also concerns on the execution and reporting of the study, concentration profiles being difficult to explain. The MAH noted BLQ values between two measurable concentrations. Upon the CHMP's request, the MAH investigated the source of the aberrant BLQ values but no root cause could be identified, neither the clinical study site nor the device seems to be a reason. However, the additionally requested sensitivity analysis showed that the impact of the aberrant BLQ concentrations is minimal with no effect on the conclusion of Study CRD1003. Hence, the issue was not further pursued.

Study CRD1003 was a two-stage adaptive design bioequivalence study in which two devices were compared to the reference device. There are several methods for controlling the Type I error, and the current EU bioequivalence guideline does not provide a definite algorithm for this. The MAH's algorithm is considered suitable for controlling Type I errors, even if it does not match the currently most commonly used solution (Potvin C algorithm). Bioequivalence was calculated with WinNonLin.

From a statistical viewpoint, there are two multiplicity issues due to tighter confidence interval deriving from the two-stage design, and due to multiple comparisons. The applied statistical procedure handled the first issue, but not the second one whereas multiplicity adjustments in bioequivalence studies involving multiple products is recommended in the Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022, effective date on 25 January 2025). Upon the CHMP's request, the MAH provided additional BE evaluation with an appropriate multiplicity adjustment. The MAH used Bonferroni's method, which is statistically sound and adequately controls alpha inflation. The analysis with alpha adjustment shows that the bioequivalence criteria were met. The CHMP concluded that Study CRD1003 provides adequate evidence that the three administration modes (1×2.0 mL PFS-U, 1×2.0 mL PFS-Y and 2×1.0 mL PFS-U) are bioequivalent.

***Pharmacokinetics in the target population: Study QUASAR***

In Study QUASAR, serum concentrations of guselkumab were determined during the induction phase (Studies IS-1 and IS-2, 200 mg IV q4w) and the maintenance phase (Studies IS-1 and IS-2, 200 mg SC q4w or 100 mg SC q8w). In Studies IS-1 and IS-2, six samples were taken: three just before the infusion administrations and three 60 minutes after them. In the maintenance phase, eight samples were collected just before the next drug administration. The variability of guselkumab concentrations ranged from 40%-55%, allowing only qualitative conclusions. Serum guselkumab concentrations over time following 200 mg IV were consistent between IS-1 and IS-2. Serum guselkumab concentrations reached steady-state at approximately Weeks M-8 and M-12 following maintenance treatment with guselkumab 200 mg SC q4w and 100 mg SC q8w. Median serum guselkumab concentrations tended to decrease with increasing body weight.

***Population Pharmacokinetic Analysis***

The POP-PK report is compliant with the Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06) and the final model is considered valid. The observed serum concentration-time data for guselkumab were adequately described by a 2-compartment linear Pop PK model with first-order absorption and first-order elimination with IIV on CL, V2, V3, and F1. However, the CHMP noted that in the study of psoriasis patients, a one-compartment PK model with first-order absorption and first-order elimination was selected as the structural PK model to describe the serum concentration versus time profile of guselkumab following SC injections.

Furthermore, the estimated absorption rate constant in psoriasis patients was 1.11/day, while in the present report it is 0.123. Upon the CHMP's request, the MAH explained that the differences between the previous and current POP-PK models were due to the fact that when the one-compartment model was developed, only SC data were available. However, in both induction phases of study QUASAR 1 and 2 and Study Galaxy, guselkumab was administered IV which allowed to develop a better absorption model. From a pharmacokinetic viewpoint, the MAH's explanation is acceptable to the CHMP.

Body weight was shown to have a statistically significant effect on clearance. The MAH considers the effect of body weight on clearance (and the volume of distribution) as having no practical significance because no trend-like relationship can be observed between therapeutic effectiveness and body weight. This is agreed by the CHMP.

***PK/PD Modelling***

*Induction Phase*

The mechanistic relationship between the parameters measuring the clinical effect during the induction phase and the concentration is considered unclear. The presented Exposure-Response model in the induction phase raised concerns since the best predictor of the effect is not the concentration measured at the end of the induction period (Ctrough) but the estimated Cl or Thalf life in that particular patient. To explain the correlation between half-life and clinical effect, the MAH assumes a latent parameter that affects both the effect and the concentration. Although inflammation can undoubtedly affect elimination, according to the POP-PK analysis, the effect of CRP, which indicates inflammation, is minimal. Since no latent factor could be identified from the POP-PK analysis, one potential candidate was the target threshold model previously described for ustekinumab. Upon the CHMP's request, the MAH provided an additional threshold model, using ROC curve analysis. Median Ctrough, week 12 of the 200 mg IV q4w treatment group (8.42 µg/mL) is above the estimated threshold concentrations of clinical remission (6.56 µg/mL) and endoscopic healing (6.85 µg/mL) at Week I 12 estimated by the ROC analysis. Therefore, a majority of participants were above these thresholds.

*Maintenance Phase*

In the maintenance phase, the clinical response rate depends on Ctrough at Week 44. However, the fitted model predicts that the 200 mg sc dose is already in the plateau section of the E-R curve, which is not correct. For those patients who were classified by endoscopy as having extensive damage, the healing rate in the highest concentrations is more than 80%, while the value estimated by the model is less than 50% suggesting a clear trend of increasing healing with higher concentration in the extensive group. However, according to the model, the predicted effect remains constant. The model cannot return the trend difference between the two groups. Similarly, the model consistently underestimates the effect in clinical remission.

Model-predicted response rates for clinical remission and endoscopic healing at Week 44 at 100 mg SC q8w and 200 mg SC q4w regimens stratified by relevant covariates highlight problematic aspects of the suggested E-R model. While the clinical response depends on whether the disease is extensive or limited, this aspect is not well handled by the model. The model generally underestimates the efficacy when the disease is limited and overestimates the efficacy for the extensive disease.

The CHMP noted the limitations of the model-predicted response. The MAH clarified that no response-dependent dosing schedule after starting the maintenance period is recommended. Hence, since the model predicted response would be to gain more insight into the therapeutic response-dependent dosage administration schedule, the issue was not further pursued by the CHMP.

***Pharmacodynamics – Biomarkers***

The biomarker results, especially the tissue transcriptomics results based on tissue biopsy, confirmed the mode of action of guselkumab and dose recommendation at the molecular level.

IL-23-dependent gene expression activity clearly differentiates the responder patient group from non-responders (NR). In contrast, no difference can be seen between the dose groups in the responder population. The reasons for non-response are not understood, but if a patient is a responder, then the extent of response is independent of the dose. At molecular level, at least, the maximum pharmacological effect can be achieved even with lower 100 mg dose schedule. Standard (CRP and fecal calprotectin), IL-23-dependent biomarkers (IL-22, IL-17A, and IFNγ) and gene expression did not show concentration dependent change, there was no difference between the 200 mg IV and 400 mg IV induction dose groups. Therefore, the guselkumab effect even at 200 mg IV must be at a plateau. This observation supports the MAH's choice to set the maximum dose to 200 mg.

Tissue gene expression changes show that some non-responders at the end of the 12-week induction period had a definite biomarker response later in the Week 24.

Guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23 mediated signalling, activation and cytokine cascades. IL23A gene expression in colon tissue confirmed elevated expression at baseline in UC compared with non-IBD healthy controls, which was reduced upon guselkumab induction treatment at Week I-12 in participants from combined guselkumab induction dose groups.

***Immunogenicity***

In the analyses in patients with UC, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralizing, which equates to 2% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or the development of injection-site reactions. The SmPC Section 4.8 is updated accordingly. These findings on immunogenicity in UC patients are in accordance with previous clinical studies in psoriasis patients.

The MAH has taken the opportunity to update Section 5.2 of the SmPC with the absolute bioavailability of guselkumab following a single 100 mg subcutaneous injection estimated to be approximately 49% in healthy subjects. This is agreed by the CHMP as supported by the results of Study NAP1001 and assessed in the iMA.

In UC studies, concomitant use of immunomodulators (eg, azathioprine [AZA]) or corticosteroids did not appear to influence the safety or efficacy of guselkumab. The SmPC section 4.5 is updated accordingly.

## 2.6.4. Conclusions on clinical pharmacology

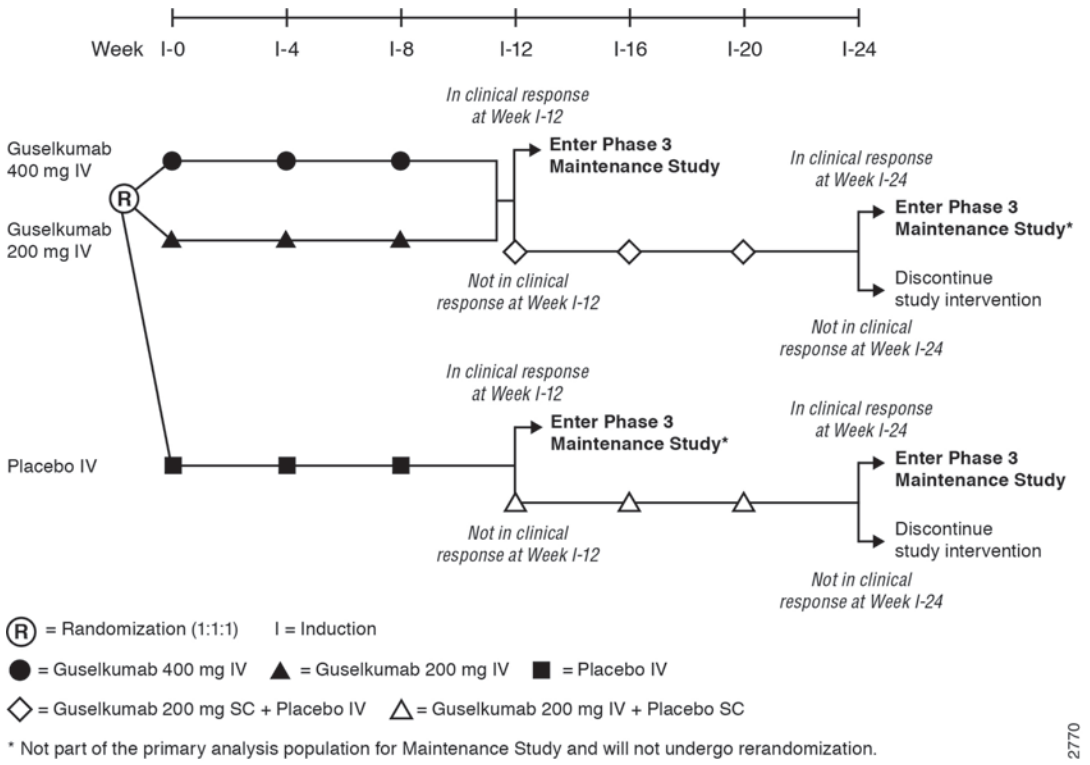
The pharmacokinetics of guselkumab in the UC population is sufficiently characterised and does not differ from the known profile of guselkumab. Dose selection of 200 mg i.v. Q4W in the induction phase is sufficiently supported by the target threshold model and biomarker data. The findings on immunogenicity in UC patients are in accordance with previous clinical studies in psoriasis patients.

## 2.6.5. Clinical efficacy

### *2.6.5.1. Dose response study(ies)*

QUASAR IS-1 was a Phase 2b dose-ranging induction study designed to evaluate the efficacy and safety of guselkumab IV induction in adult participants with moderately to severely active UC and to select the guselkumab IV induction dose regimen for confirmatory evaluation in the Phase 3 induction study (IS-2) (Figure 15).

**Figure 15: Study Schema CNTO1959UCO3001 Phase 2b IS-1 (Dose-ranging Study)**




**Methods**

**Study Participants**

The target population consisted of adult men and women ≥18 years of age with moderately to severely active UC who had demonstrated an inadequate response or failure to tolerate conventional (ie, 6-MP, AZA, or corticosteroids) or ADT (ie, TNF$\alpha$ antagonists, vedolizumab, or tofacitinib). The study enrolled participants with baseline (Week I-0) modified Mayo score of 4 to 9, inclusive, with a modified Mayo Score of 4 capped at ≤5% of the total population.

The primary analysis population included randomized participants with a modified Mayo score of 5 to 9 at induction baseline. In addition, participants were required to have a Mayo rectal bleeding subscore ≥ 1 at baseline and a screening endoscopy with ≥2 on the endoscopy subscore of the Mayo score as obtained during the central review of the video endoscopy.

Dose-finding induction study IS-1 and main induction study IS-2 shared their inclusion and exclusion criteria.

**Treatments**

Participants were randomized in a 1:1:1 ratio to receive guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo IV at Week I-0. Participants were evaluated at Week I-12 and assigned further study intervention based on clinical response status at Week I-12.

Participants who achieved clinical response during IS-1, were eligible to enter the Maintenance Study.

Participants initially randomized to placebo who were not in clinical response at Week I-12 crossed over to guselkumab and received 3 doses of guselkumab 200 mg IV at Weeks I-12, I-16, and I-20.

Participants initially randomized to guselkumab who were not in clinical response at Week I-12 received 3 doses of guselkumab 200 mg SC at Weeks I-12, I-16, and I-20.

**Objectives**

*Primary objectives*

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.
- To evaluate the dose-response of guselkumab and to inform induction dose selection for the Phase 3 Induction Study.

*Secondary objectives*

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

**Outcomes/endpoints**

Primary endpoint in this study is clinical response at Induction Week 12 (Week I-12).

Major secondary endpoints are:

- Clinical remission at Week I-12.
- Symptomatic remission at Week I-12.
- Endoscopic healing at Week I-12.
- Histologic-endoscopic mucosal healing at Week I-12.
- Endoscopic normalization at Week I-12.

**Sample size**

The minimum sample size for Induction Study 1 was 150 participants, up to a maximum of 390 participants. A total of 328 participants were randomized in this induction study. Among these participants, 313 participants were treated and had a modified Mayo score of 5 to 9, which comprised the Full Analysis Set (primary analysis population).

**Randomisation and blinding (masking)**

Participants were randomized in a 1:1:1 ratio to receive guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo IV at Week I-0 using permuted block randomization stratified by ADT-failure status (Yes/No), region (Eastern Europe, Asia, or Rest of World), and concomitant use of corticosteroids at baseline (Yes/No).

The investigator was not provided with randomization codes. The codes were maintained within the Interactive Web Response System, which had the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment assignment (eg, study intervention serum concentrations, antibodies to study intervention) were handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimized. This included making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the study unblinding.

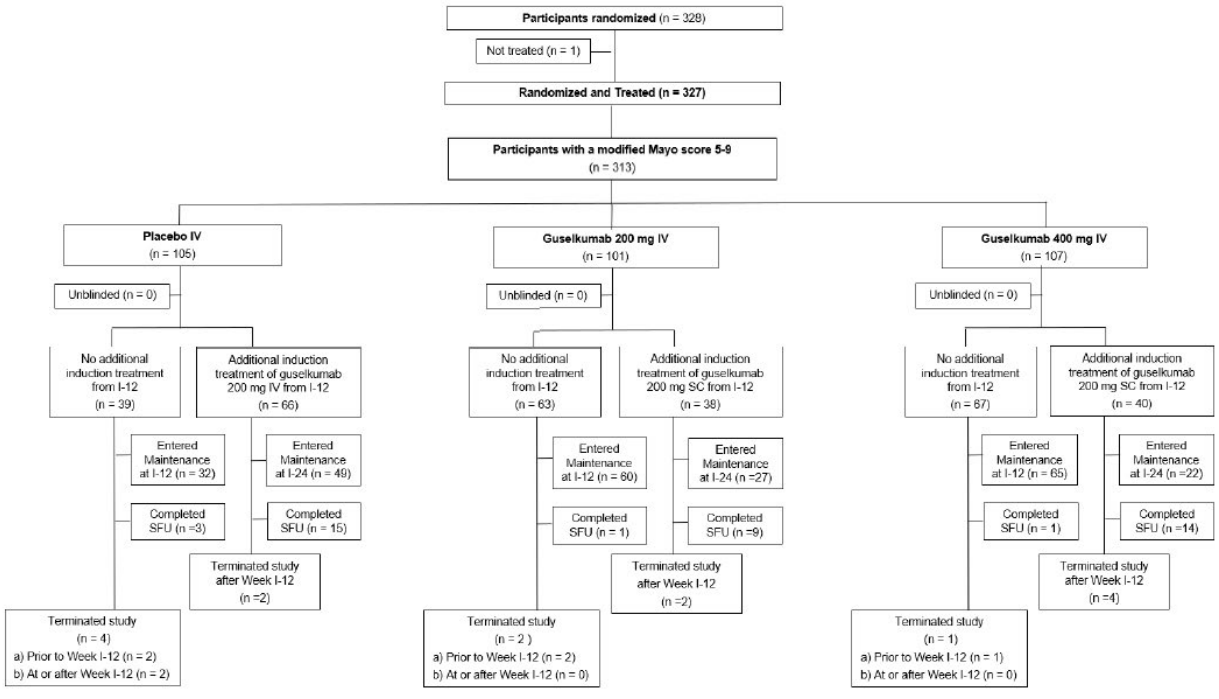
**Statistical methods**

Descriptive statistics (ie, N, mean, median, SD, IQ range, minimum, and maximum) was used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. Analyses suitable for categorical data (eg, chi-square tests, CMH chi-square tests, or logistic regression, as appropriate) were used to compare the proportions of participants achieving selected endpoints (eg, clinical response). In cases of rare events, Fisher's exact test was used for treatment comparisons. In cases of small sample size, t-test was used for treatment comparisons.

A multiple testing procedure was used to control the Type-I error at a 2-sided 0.05 significance level over the comparisons for the primary endpoint; the other endpoints were not adjusted for multiplicity and nominal p-values were presented for these analyses.

**Results**

**Participant flow**




Abbreviations: SFU = safety follow-up

**Conduct of the study**

Protocol amendment and protocol compliance for the QUASAR programme are presented and discussed in Section 2.6.5.2.

**Baseline data**

Baseline data are presented for the IS-1 and IS-2 studies in Section 2.6.5.2.

**Outcomes and estimation**

**Table 15: Number of Participants Who Achieved Selected Efficacy Endpoints (CNTO1959UCO3001 Phase 2b Induction Study 1; Full Analysis Set)**

| | | Guselkumab | |
|---|---|---|---|
| | Placebo IV | 200 mg IV | 400 mg IV |
| Full Analysis Set | 105 | 101 | 107 |
| **Primary Endpoint** | | | |
| Clinical response[a] at Week I-12 | 29 (27.6%) | 62 (61.4%)‡ | 65 (60.7%)‡ |
| **Major Secondary Endpoints** | | | |
| Clinical remission[b] at Week I-12[c] | 10 (9.5%) | 26 (25.7%)† | 27 (25.2%)† |
| Symptomatic remission[d] at Week I-12 | 21 (20.0%) | 50 (49.5%)‡ | 51 (47.7%)‡ |
| Endoscopic healing[e] at Week I-12 | 13 (12.4%) | 31 (30.7%)† | 33 (30.8%)‡ |
| Histologic-endoscopic mucosal healing[f] at Week I-12 | 9 (8.6%) | 21 (20.8%)* | 29 (27.1%)‡ |
| Endoscopic normalization[g] at Week I-12 | 7 (6.7%) | 18 (17.8%)* | 15 (14.0%) |
| **Other Endpoints[h]** | | | |
| IBDQ remission[i] at Week I-12 | 28 (26.7%) | 53 (52.5%)‡ | 59 (55.1%)‡ |
| Symptomatic remission[d] at Week I-4 | 5 (4.8%) | 18 (17.8%)† | 26 (24.3%)‡ |
| Fatigue response[j] at Week I-12 | 31 (29.5%) | 45 (44.6%)* | 43 (40.2%) |
| Symptomatic remission[d] at Week I-2 | 4 (3.8%) | 10 (9.9%) | 13 (12.1%)* |

‡p<0.001; †p<0.01; *p<0.05. **All p-values (except for the primary endpoint) are nominal**. p-values were based on the Cochran-Mantel-Haenszel chi-square test.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

a Clinical response=a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

b Clinical remission=a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

c The primary endpoint in the Phase 3 CNTO1959UCO3001 Induction Study 2 was clinical remission at Week I-12.

d Symptomatic remission=a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

e Endoscopic healing (improvement)=an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

f Histologic-endoscopic mucosal healing (improvement)=achieving a combination of histologic healing and endoscopic healing.

g Endoscopic normalization (remission)=an endoscopy subscore of 0.

h Other endpoints which were defined as major secondary endpoints in IS-2.

i IBDQ remission=total Inflammatory Bowel Disease Questionnaire score ≥170.

j Fatigue response=a ≥7-point improvement from baseline in PROMIS-Fatigue Short Form 7a.

**Ancillary analyses**

Subgroup analysis are presented for the pooled IS-1 and IS-2 studies in Section 2.6.5.2.

### *2.6.5.2. Main study(ies)*

#### 2.6.5.2.1. Study CNTO1959UCO3001 IS-2 (QUASAR IS-2)

***Methods***

- **Study Participants**

The target population consisted of adult men and women ≥18 years of age with moderately to severely active UC who had demonstrated an inadequate response or failure to tolerate conventional (ie, 6-MP, AZA, or corticosteroids) or ADT (ie, TNF $\alpha$ antagonists, vedolizumab, or tofacitinib). The study enrolled

participants with baseline (Week I-0) modified Mayo score of 4 to 9, inclusive, with a modified Mayo Score of 4 capped at ≤5% of the total population.

Main exclusion criteria were:

1. Severe extensive colitis
2. UC limited to the rectum only or to <20 cm of the colon.
3. Presence of a stoma.
4. Presence or history of a fistula.
5. Require, or required within the 2 months before screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study intervention treatment.
6. Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction.
7. History of extensive colonic resection (eg, less than 30 cm of colon remaining).
8. History of colonic mucosal dysplasia.
9. Presence on screening endoscopy of adenomatous colonic polyps, if not removed before study entry, or history of adenomatous colonic polyps that were not removed.
10. Diagnosis of indeterminate colitis, microscopic colitis, ischemic colitis, or Crohn's disease or clinical findings suggestive of Crohn's disease.
11. Stool culture or other examination positive for an enteric pathogen, including Clostridium difficile toxin, within 4 months before the first dose of study intervention, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.

- **Treatments**

From Week I-0 Through Week I-8, participants were randomized to 1 of 2 study treatment groups:

- Guselkumab 200 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
- Placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

From Week I-12 through Week I-20, additional Induction Study intervention administration after Week I-8 was based on clinical_response status at Week I-12:

- Guselkumab: For participants who received 3 IV guselkumab doses (200 mg), subsequent study intervention was based on clinical response status at Week I-12 as follows:
    - Guselkumab clinical nonresponders at Week I-12 received guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV was also administered at Weeks I-12, I-16, and I-20 to maintain the blind.
    - Guselkumab clinical responders at Week I-12: Participants entered the Maintenance Study.
- Placebo: For participants who received 3 IV placebo doses, subsequent study intervention was based on clinical response status at Week I-12 as follows:

- Placebo clinical nonresponders at Week I-12 received guselkumab 200 mg IV at Weeks I-12, I-16, and I-20. Placebo SC was also administered at Weeks I-12, I-16, and I-20 to maintain the blind.
- Placebo clinical responders at Week I-12: Participants entered the Maintenance Study.

Participants who were not in clinical response at Week I-24 did not receive further study intervention and completed a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

- **Objectives**

The primary objectives of this study in participants with moderately to severely active UC were:

- To evaluate the efficacy of guselkumab as induction therapy.
- To evaluate the safety of guselkumab as induction therapy.

The secondary objectives of this study in participants with moderately to severely active UC were:

- To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
- To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin

- **Outcomes/endpoints**

The primary outcome was Clinical remission at Week I-12, where participants were considered to have achieved clinical remission if they fulfilled the clinical remission criteria based on the modified Mayo Score components.

The major secondary endpoints were as follows:

- Symptomatic remission at Week I 12
- Endoscopic healing at Week I 12
- Clinical response at Week I 12
- Symptomatic remission at Week I 4
- IBDQ remission at Week I 12
- Histologic-endoscopic mucosal healing at Week I 12
- Fatigue response at Week I 12
- Symptomatic remission at Week I 2
- Endoscopic normalization at Week I 12

PRO endpoints were as follows:

- PROMIS-Fatigue SF-7a T-score
- Fatigue response at Week I 12 (major secondary endpoint)
- IBDQ total score
- IBDQ remission at Week I 12 (major secondary endpoint)
- Participants with bowel urgency severity at induction baseline (Q24≤5)
- Participants with a ≥2-point improvement in bowel urgency severity at Week I 12

- Participants with a ≥2-point improvement in impact of bowel urgency at Week I 12
- Participants with a ≥2-point improvement in abdominal pain at Week I 12
- PROMIS 29 PCS T-score
- Participants with ≥7-point improvement in PROMIS 29 PCS at Week I 12
- PROMIS 29 MCS T-score
- Participants with ≥7-point improvement in PROMIS 29 MCS at Week I 12
- EQ-VAS

- **Sample size**

The primary efficacy analysis set for QUASAR IS-2 consisted of 701 treated participants: 421 participants in the guselkumab 200 mg IV group and 280 participants in the placebo group.

- **Randomisation and Blinding (masking)**

Participants were randomized in a 3:2 ratio to guselkumab 200 mg IV or placebo IV administered at Weeks I-0, I-4, and I-8.

Participants were allocated to a treatment group using permuted block randomization stratified by ADT-failure status (ie, inadequate response or failure to tolerate TNF$\alpha$ antagonists, vedolizumab, or tofacitinib) (Yes/No), region (Eastern Europe, Asia, or Rest of World), and concomitant use of corticosteroids at baseline (Yes/No).

Blinding measures were the same within the QUASAR programme and are described for Study IS-1 (Section 2.6.5.1. ).

- **Statistical methods**

**Analysis sets**

*Randomized Analysis Sets*

- Randomized Analysis Set: all participants who were randomized in the study.
- Randomized Modified Mayo 5-9 Analysis Set: all participants randomized in the study with a baseline modified Mayo Score of 5 to 9.
- Week I-12 Treated Analysis Set: participants who were not in clinical response at Week I-12 as determined by the IWRS and who received study intervention at or after Week I-12.

*Efficacy Analysis Sets*

- Full Analysis Set: all randomized participants with a baseline modified Mayo Score of 5 to 9 who received at least 1 (partial or complete) dose of study intervention.
- Efficacy All Treated Analysis Set: all randomized participants (regardless of baseline modified Mayo Score) who received at least 1 (partial or complete) dose of study intervention.
- Week I-12 Clinical Nonresponder Analysis Set: participants with a baseline modified Mayo Score of 5 to 9 who were not in clinical response at Week I-12 and received study intervention at or after Week I-12.

Participants were analyzed according to their randomized or assigned study intervention regardless of the study intervention they actually received.

**Statistical analyses**

Descriptive statistics (ie, N, mean, median, SD, IQR, minimum, and maximum) were used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. Graphical data displays (eg, line plots) were also used to summarize the data.

Analyses suitable for categorical data (eg, chi-square tests, CMH tests, or logistic regression, as appropriate) were used to compare the proportions of participants achieving selected endpoints (eg, clinical response). In cases of rare events, Fisher' s exact test was used for treatment comparisons.

Continuous response parameters measured at more than 1 postbaseline visit were compared using an MMRM model (unless otherwise specified). If the normality assumption was in question, an appropriate transformation was implemented before fitting the MMRM model.

Continuous response parameters measured at only 1 postbaseline visit were compared using an ANOVA or ANCOVA, unless otherwise specified. In cases of small sample size, t-test was used for treatment comparisons. The time to event endpoints were compared using a stratified log-rank test or a log-rank test.

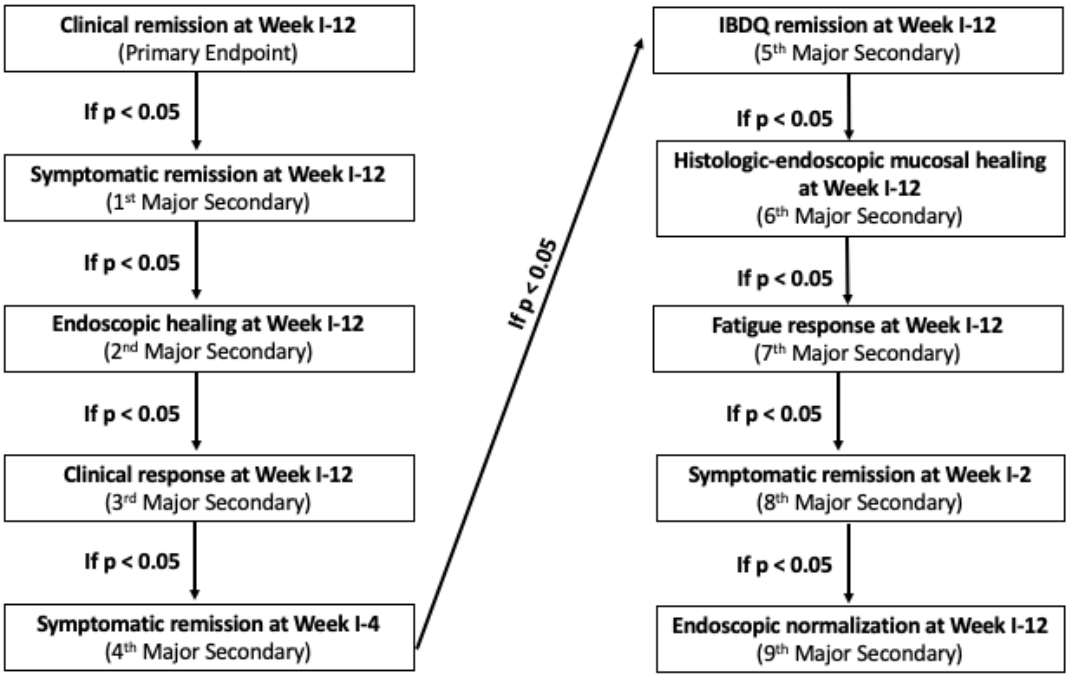
Planned subgroup analyses

The primary endpoint was evaluated for the following main subgroups:

- region (Eastern Europe, Asia, RoW)
- demography-related: baseline age, gender, race (Caucasian/non-Caucasian), baseline bodyweight
- UC-related subgroups: disease duration, extent of disease, severity of disease by Mayo score, baseline Mayo endoscopy subscore, extraintestinal manifestation (yes/no), CRP (above/below 3 mg/L, fecal calprotectin (above/below 250 mg/kg)
- UC-related concomitant medication: oral 5-ASA, oral corticosteroid, 6-MP/AZA/MTX
- UC-related medication history: ADT-failure, one, two or three ADT class failures, biologic failure, corticosteroid dependence/refractory/intolerance

*Error probabilities, adjustment for multiplicity and interim analyses*

**Figure 16: Global Testing Procedure for the Primary and Major Secondary Endpoints (CNTO1959UCO3001 Phase 3 Induction Study 2)**



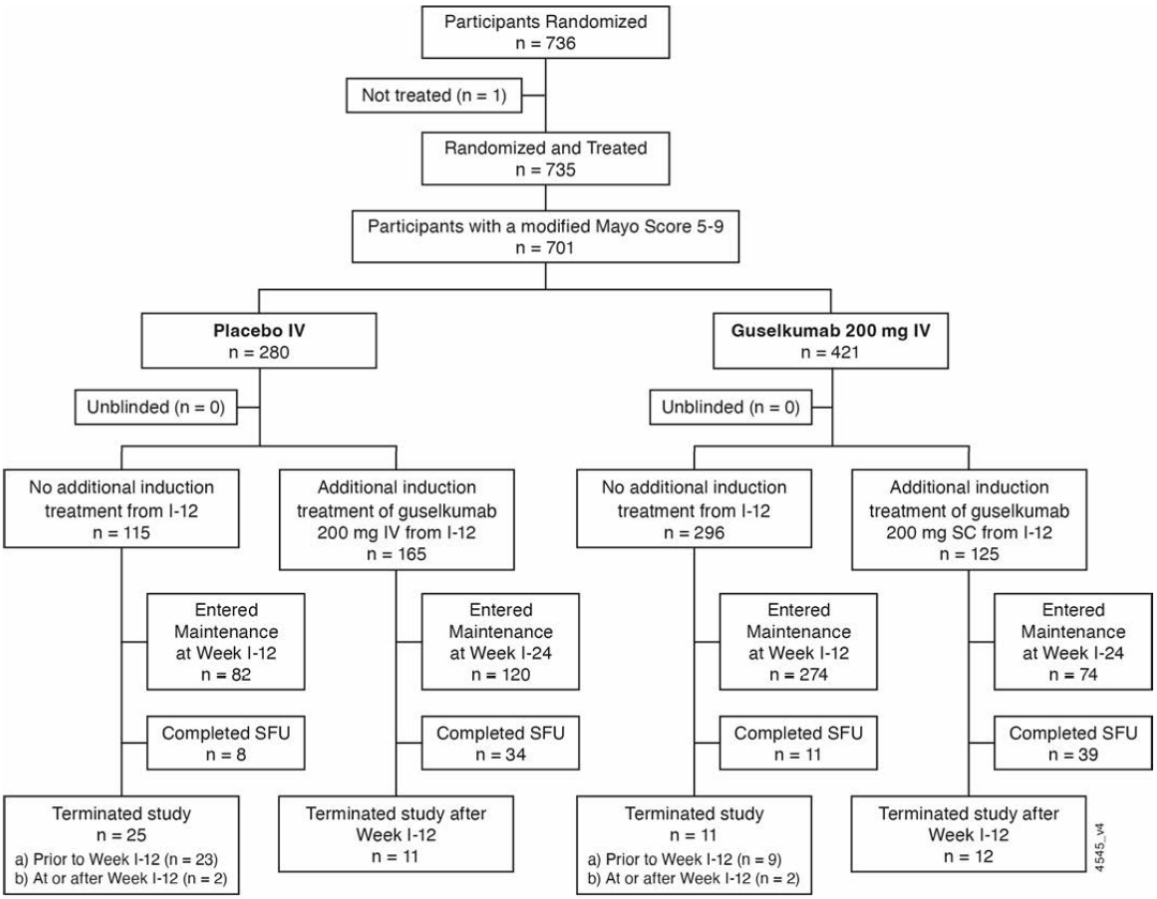

*Changes from protocol-specified analyses*

Amendment of the SAP of the QUASAR studies was dated to 9 September 2021. The significant updates were to accomodate the regulatory query of the inclusion of UC patients with modified Mayo scores between 5 and 9 (both inclusive) instead of the original range of 4-9 and to remove Region' as a stratification variable in all efficacy analyses

***Results***

- **Participant flow**

**Figure 17: Participant flow, QUASAR IS-2**




- **Recruitment**

Study Initiation Date: 26 September 2019 (first site was opened)

Study Completion Date: Not applicable, study is ongoing

Data Cutoff Date: 12 January 2023 (date of last observation recorded as part of the database lock for Induction Study 2)

- **Conduct of the study**

*Protocol amendments*

- Amendment 1 (08 January 2020): Updates of the induction dose and maintenance regimens
- Amendment 2 (03 August 2021): Primary analysis population was modified to include only randomized participants with a modified Mayo Score of 5 through 9 at induction baseline. Targeted enrolment for the programme was increased, the programme also enrolled participants with a modified Mayo Score of 4 (≤5%). Major secondary endpoints (IBDQ remission and fatigue response) were added to Induction Study 2 and the Maintenance Study.
- Amendment 3 (12 September 2022): Extension of the duration of the long-term extension of the Maintenance Study to approximately 4 years.

- Country-specific amendments for Russia and New Zealand were submitted.

*Protocol deviations*

Through Week I-12, 68 (9.7%) participants in the Full Analysis Set had Major Protocol Deviations (MPDs). The most common categories of MPDs were due to participants who entered the study but did not satisfy entry criteria (39[5.6%]) and "other" (27 [3.9%]).

- **Baseline data**

**Table 16: Summary of Induction Baseline Demographics, UC Disease Characteristics, and UC-related Concomitant Medications and Medication History (CNTO1959UCO3001)**

| | Induction Study 1 (Phase 2b) | Induction Study 2 (Phase 3) | Maintenance (Phase 3) |
|---|---|---|---|
| Primary analysis population | 313 | 701 | 568 |
| **Demographic Characteristics** | | | |
| Median Age (years) | 39.0 | 39.0 | 39.0 |
| ≥65 years | 6.4% | 5.8% | 6.2% |
| Sex | | | |
| Female | 40.9% | 43.1% | 45.2% |
| Male | 59.1% | 56.9% | 54.8% |
| Region | | | |
| Asia | 22.7% | 20.3% | 19.0% |
| Eastern Europe | 48.9% | 42.2% | 48.4% |
| Rest of World | 28.4% | 37.5% | 32.6% |
| Latin America | 1.3% | 6.0% | 4.4% |
| North America | 5.1% | 5.0% | 5.1% |
| Western Europe | 19.5% | 16.0% | 16.0% |
| Other | 2.6% | 10.6% | 7.0% |
| Race | | | |
| American Indian or Alaskan Native | 0 | 0.1% | 0 |
| Asian | 23.6% | 21.4% | 20.4% |
| Black or African American | 1.0% | 1.0% | 1.1% |
| Native Hawaiian or Other Pacific Islander | 0 | 0.3% | 0.2% |
| White | 71.6% | 72.5% | 73.2% |
| Multiple | 0.3% | 0.1% | 0.2% |
| Not reported | 3.5% | 4.6% | 4.9% |
| Ethnicity | | | |
| Hispanic or Latino | 4.2% | 6.7% | 4.9% |
| Not Hispanic or Latino | 91.7% | 86.6% | 88.7% |
| Not reported | 4.2% | 6.7% | 6.3% |
| Median weight (kg) | 69.90 | 70.60 | 70.00 |
| Median height (cm) | 170.00 | 170.10 | 170.05 |
| **UC disease characteristics** | | | |
| Median UC disease duration (years) | 5.80 | 5.31 | 5.39 |
| Extent of UC disease | | | |
| Limited to left side of colon | 51.1% | 52.2% | 54.8% |
| Extensive | 48.9% | 47.8% | 45.2% |
| Mean modified Mayo score | 7.0 | 6.9 | 6.9 |
| Severity of UC disease | | | |
| Moderate (modified Mayo score of 5-6) | 30.4% | 35.5% | 36.1% |
| Severe (modified Mayo score of 7-9) | 69.6% | 64.5% | 63.9% |
| Severity of endoscopy subscore | | | |
| Moderate (endoscopy subscore=2) | 30.0% | 32.1% | 33.6% |
| Severe (endoscopy subscore=3) | 70.0% | 67.9% | 66.4% |

| | Induction Study 1 (Phase 2b) | Induction Study 2 (Phase 3) | Maintenance (Phase 3) |
|---|---|---|---|
| Primary analysis population | 313 | 701 | 568 |
| Median CRP (mg/L) | 4.6 | 4.2 | 3.9 |
| Elevated CRP (>3 mg/L) | 62.7% | 58.8% | 57.8% |
| Median fecal calprotectin (mg/kg) | 1,564.0 | 1,641.0 | 1,605.0 |
| Elevated fecal calprotectin (>250 mg/kg) | 89.5% | 89.6% | 87.9% |
| Median albumin (g/L) | 43.0 | 43.0 | 43.0 |
| **UC-related concomitant medication** | 90.4% | 87.3% | 87.7% |
| Oral corticosteroid use | 39.9% | 43.1% | 40.0% |
| Budesonide | 6.1% | 7.0% | 5.6% |
| Beclomethasone dipropionate | 0.6% | 1.1% | 0.9% |
| Other corticosteroid use | 33.9% | 35.1% | 33.8% |
| Immunomodulatory drugs | 22.0% | 20.8% | 22.2% |
| 6-MP/AZA | 21.7% | 19.7% | 21.5% |
| Methotrexate | 0.3% | 1.1% | 0.7% |
| Oral aminosalicylates | 77.3% | 72.5% | 77.1% |
| **UC-related medication history** | | | |
| Participants with inadequate response, intolerance, or dependence to corticosteroids and/or 6-MP/AZA | 93.3% | 93.2% | 93.8% |
| Participants without ADT failure | 52.7% | 50.9% | 57.7% |
| ADT-naïve[a] | 93.3% | 95.0% | 94.2% |
| ADT-experienced, without documented failure[a] | 6.7% | 5.0% | 5.8% |
| Participants with ADT-failure | 47.3% | 49.1% | 42.3% |
| At least one anti-TNF[b] | 89.9% | 87.5% | 87.9% |
| Vedolizumab[b] | 52.7% | 54.1% | 49.2% |
| Tofacitinib[b] | 20.9% | 18.0% | 20.0% |
| 1 ADT class[b] | 50.7% | 52.6% | 57.5% |
| anti-TNF only[b] | 41.2% | 41.0% | 46.3% |
| Vedolizumab only[b] | 6.8% | 9.9% | 9.6% |
| Tofacitinib only[b] | 2.7% | 1.7% | 1.7% |
| ≥2 ADT classes[b] | 49.3% | 47.4% | 42.5% |
| 2 ADT classes[b] | 35.1% | 35.2% | 27.9% |
| 3 ADT classes[b] | 14.2% | 12.2% | 14.6% |

Notes: Baseline summaries are based on values at induction baseline.
The primary analysis population includes only participants with modified Mayo score of 5 to 9 at induction baseline.
a Denominator is participants without a history of ADT failure.
b Denominator is participants with a history of ADT failure.

- **Numbers analysed**

A total of 1005 participants were screened for study entry and 736 of these participants were randomized in 240 centers across 32 countries/territories. The majority of randomized participants were from Eastern Europe (41.4%), with the remainder distributed across Asia (20.5%), and Rest of World (38.0%, across Western Europe, North America, Latin America and other [including Australia, Israel, and New Zealand]). There were 67 screened participants who were not captured as screened in the final DBL for this study.

- **Outcomes and estimation**

**Full analysis set**

*Primary and Major Secondary Endpoints*

**Table 17: Number of Participants Who Achieved the Primary and Major Secondary Endpoints**

*(CNTO1959UCO3001 Phase 3 Induction Study 2; Full Analysis Set)*

| | Placebo IV | Guselkumab 200 mg IV |
|---|---|---|
| Full Analysis Set | 280 | 421 |
| Primary Endpoint | | |
| Clinical remission[a] at Week I-12 | 22 (7.9%) | 95 (22.6%)‡ |
| Major Secondary Endpoints | | |
| Symptomatic remission[b] at Week I-12 | 58 (20.7%) | 210 (49.9%)‡ |
| Endoscopic healing[c] at Week I-12 | 31 (11.1%) | 113 (26.8%)‡ |
| Clinical response[d] at Week I-12 | 78 (27.9%) | 259 (61.5%)‡ |
| Symptomatic remission[b] at Week I-4 | 36 (12.9%) | 95 (22.6%)‡ |
| IBDQ remission[e] at Week I-12 | 83 (29.6%) | 216 (51.3%)‡ |
| Histologic-endoscopic mucosal healing[f] at Week I-12 | 21 (7.5%) | 99 (23.5%)‡ |
| Fatigue response[g] at Week I-12 | 60 (21.4%) | 173 (41.1%)‡ |
| Symptomatic remission[b] at Week I-2 | 26 (9.3%) | 51 (12.1%) |
| Endoscopic normalization[h] at Week I-12 | 14 (5.0%) | 63 (15.0%)‡ |

‡p<0.001; †p<0.01; *p<0.05. p-values were based on the Cochran-Mantel-Haenszel chi-square test.

Notes: **p-value for endoscopic normalization is nominal.**

Includes only participants with a modified Mayo score of 5-9 at induction baseline.

a Clinical remission=a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

b Symptomatic remission=a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

c Endoscopic healing (improvement)=an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

d Clinical response=a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

e IBDQ remission=total Inflammatory Bowel Disease Questionnaire score ≥170.

f Histologic-endoscopic mucosal healing (improvement)=achieving a combination of histologic healing and endoscopic healing.

g Fatigue response=a ≥7-point improvement from baseline in PROMIS-Fatigue Short Form 7a.

h Endoscopic normalization (remission)=an endoscopy subscore of 0.

*Endoscopy and Histology at Week I 12*

**Table 18: Number of Participants Who Achieved Other Endoscopic and Histologic Efficacy Endpoints (CNTO1959UCO3001 Phase 3 Induction Study 2; Full Analysis Set)**

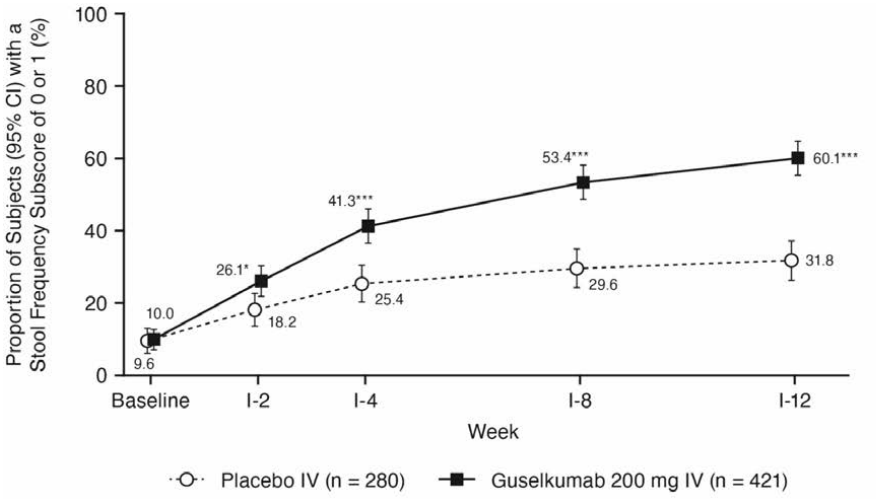
| | Placebo IV | Guselkumab 200 mg IV |
|---|---|---|
| Full Analysis Set | 280 | 421 |
| Histologic healing (ie, Geboes score ≤3.1) at Week I-12 | 60 (21.4%) | 189 (44.9%)‡ |
| Histologic healing at Week I-12 among participants without histologic healing at baseline | 42/241 (17.4%) | 159/363 (43.8%)‡ |
| Histologic remission (ie, Geboes score ≤2B.0) at Week I-12 | 52 (18.6%) | 168 (39.9%)‡ |
| Histologic-endoscopic mucosal healing (alternative definition, ie, histologic remission and endoscopic healing) at Week I-12 | 20 (7.1%) | 93 (22.1%)‡ |
| Deep histologic-endoscopic mucosal healing (improvement; ie, histologic remission and endoscopic normalization) at Week I-12 | 11 (3.9%) | 57 (13.5%)‡ |

‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal and were based on the Cochran-Mantel-Haenszel chi-square test.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

*Stool frequency subscore*

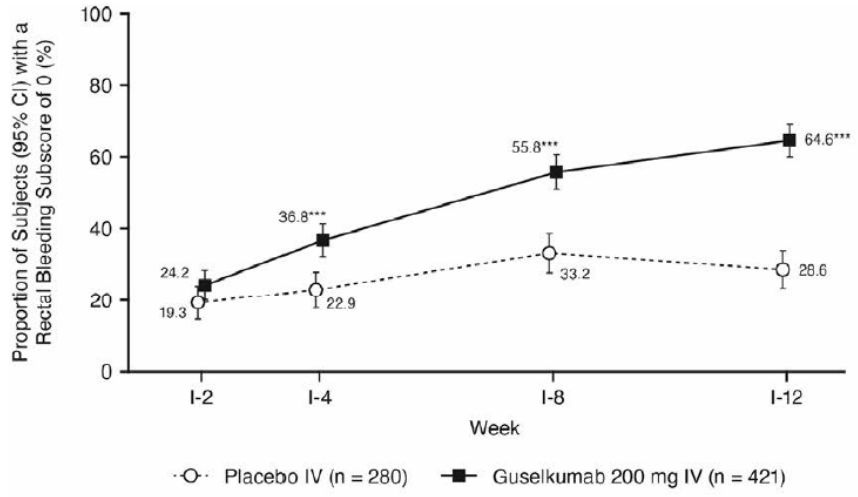
**Figure 18: Proportion of Participants With a tool Frequency Subscore of 0 or 1 Through Week I-12; Full Analysis Set (Study CNTO1959UCO3001; Induction 2)**




***p<0.001; *p≤0.05. All p-values are nominal.

*Rectal bleeding subscores*

**Figure 19: Proportion of Participants With a Rectal Bleeding Subscore of 0 Through Week I-12; Full Analysis Set (Study CNTO1959UCO3001; Induction 2)**




*Patient-reported Outcomes Through Week I-12*

**Table 19: Summary of Improvement in Patient-reported Outcomes at Week I 12 (CNTO1959UCO3001 Phase 3 Induction Study 2; Full Analysis Set)**

| | Placebo IV | Guselkumab 200 mg IV |
|---|---|---|
| Full Analysis Set | 280 | 421 |
| **PROMIS-Fatigue SF-7a T-score** | | |
| Change from baseline at Week I-12 (Mean [SD])[a] | -2.14 (7.569) | -5.71 (8.774) |
| Treatment difference in LS Means (95% CI) | | -3.7 (-5.0, -2.5)‡ |
| **Fatigue response at Week I-12** (major secondary endpoint) | | |
| Participants n (%) | 60 (21.4%) | 173 (41.1%) |
| Adjusted treatment difference (95% CI) | | 19.8% (13.1%, 26.4%)‡ |
| **IBDQ total score** | | |
| Change from baseline at Week I-12 (Mean [SD])[b] | 18.6 (36.01) | 39.0 (35.38) |
| Treatment difference in LS Means (95% CI) | | 20.5 (15.4, 25.5)‡ |
| **IBDQ remission at Week I-12** (major secondary endpoint) | | |
| Participants n (%) | 83 (29.6%) | 216 (51.3%) |
| Adjusted treatment difference in LS Means (95% CI) | | 21.9% (14.9%, 29.0%)‡ |
| **Bowel urgency severity** | | |
| Participants with bowel urgency severity at induction baseline (Q24≤5) | 233 | 362 |
| Participants with a ≥2-point improvement in bowel urgency severity at Week I-12 | 77 (33.0%) | 212 (58.6%) |
| Adjusted treatment difference (95% CI) | | 25.4% (17.8%, 33.1%)‡ |
| **Impact of bowel urgency** | | |
| Participants with impact of bowel urgency at induction baseline (Q16≤5) | 197 | 298 |
| Participants with a ≥2-point improvement in impact of bowel urgency at Week I-12 | 65 (33.0%) | 172 (57.7%) |
| Adjusted treatment difference (95% CI) | | 24.8% (16.4%, 33.3%)‡ |
| **Abdominal pain** | | |
| Participants with abdominal pain at induction baseline (Q13≤5) | 218 | 327 |
| Participants with a ≥2-point improvement in abdominal pain at Week I-12 | 72 (33.0%) | 170 (52.0%) |
| Adjusted treatment difference (95% CI) | | 19.2% (11.1%, 27.4%)‡ |
| **PROMIS-29 PCS T-score** | | |
| Change from baseline at Week I-12 (Mean [SD])[b] | 2.07 (6.302) | 4.42 (7.601) |
| Treatment difference in LS Means (95% CI) | | 2.6 (1.5, 3.6)‡ |
| Participants with ≥7-point improvement in PROMIS-29 PCS at Week I-12 | 49 (17.5%) | 127 (30.2%) |
| Adjusted treatment difference (95% CI) | | 12.8% (6.6%, 19.0%)‡ |
| **PROMIS-29 MCS T-score** | | |
| Change from baseline at Week I-12 (Mean [SD])[b] | 2.67 (7.155) | 6.00 (7.696) |
| Treatment difference in LS Means (95% CI) | | 3.4 (2.3, 4.5)‡ |
| Participants with ≥7-point improvement in PROMIS-29 MCS at Week I-12 | 58 (20.7%) | 169 (40.1%) |
| Adjusted treatment difference (95% CI) | | 19.5% (12.9%, 26.2%)‡ |
| **EQ-VAS** | | |
| Change from baseline at Week I-12 (Mean [SD])[a] | 4.6 (18.28) | 14.5 (20.25) |
| Treatment difference in LS Means (95% CI) | | 9.8 (7.2, 12.5)‡ |

* p<0.05; † p<0.01; ‡ p<0.001. p-values were nominal except for fatigue response and IBDQ remission.
Note: Includes only participants with modified Mayo score 5-9 at induction baseline.
a For change from baseline in PROMIS-Fatigue SF-7a and EQ VAS: N=260 (placebo); N=405 (guselkumab 200 mg IV).
b For change from baseline in IBDQ total score, PROMIS-29 PCS, and PROMIS-29 MCS: N=261 (placebo); N=405 (guselkumab 200 mg IV).

**Week I-12 Clinical Nonresponders**

No statistical comparisons were performed in the Week I-12 Clinical Non responder Analysis Set for this uncontrolled period from Week I-12 through Week I-24.

*Week I-12 Guselkumab Clinical Nonresponders*

Following guselkumab IV induction, additional blinded treatment with guselkumab 200 mg SC (at Weeks I-12, I-16, and I-20) was evaluated in the guselkumab Week I-12 clinical non responders:

- Clinical remission at Week I-24: 9.6%
- Clinical response at Week I-24: 55.2%
- Symptomatic remission at Week I-24: 40.8%
- Endoscopic healing at Week I-24: 12.8%
- Endoscopic normalization at Week I-24: 6.4%
- Histologic healing at Week I-24: 33.6%
- Histologic remission at Week I-24: 27.2%
- Histologic-endoscopic mucosal healing at Week I-24: 10.4%
- Deep histologic-endoscopic mucosal healing at Week I-24: 5.6%
- Mayo Score at Week I-24: -3.4
- Partial Mayo Score at Week I-24: -3.0
- Modified Mayo Score at Week I-24: -2.5
- Stool frequency subscores at Week I-24: -1.1
- Rectal bleeding subscores at Week I-24: -1.0

*Week I-12 Placebo Clinical Nonresponders*

The clinical benefit of blinded treatment with guselkumab 200 mg IV (administered at Weeks I-12, I-16, and I-20) at Week I-24 in the Week I-12 placebo clinical non responder group was as follows:

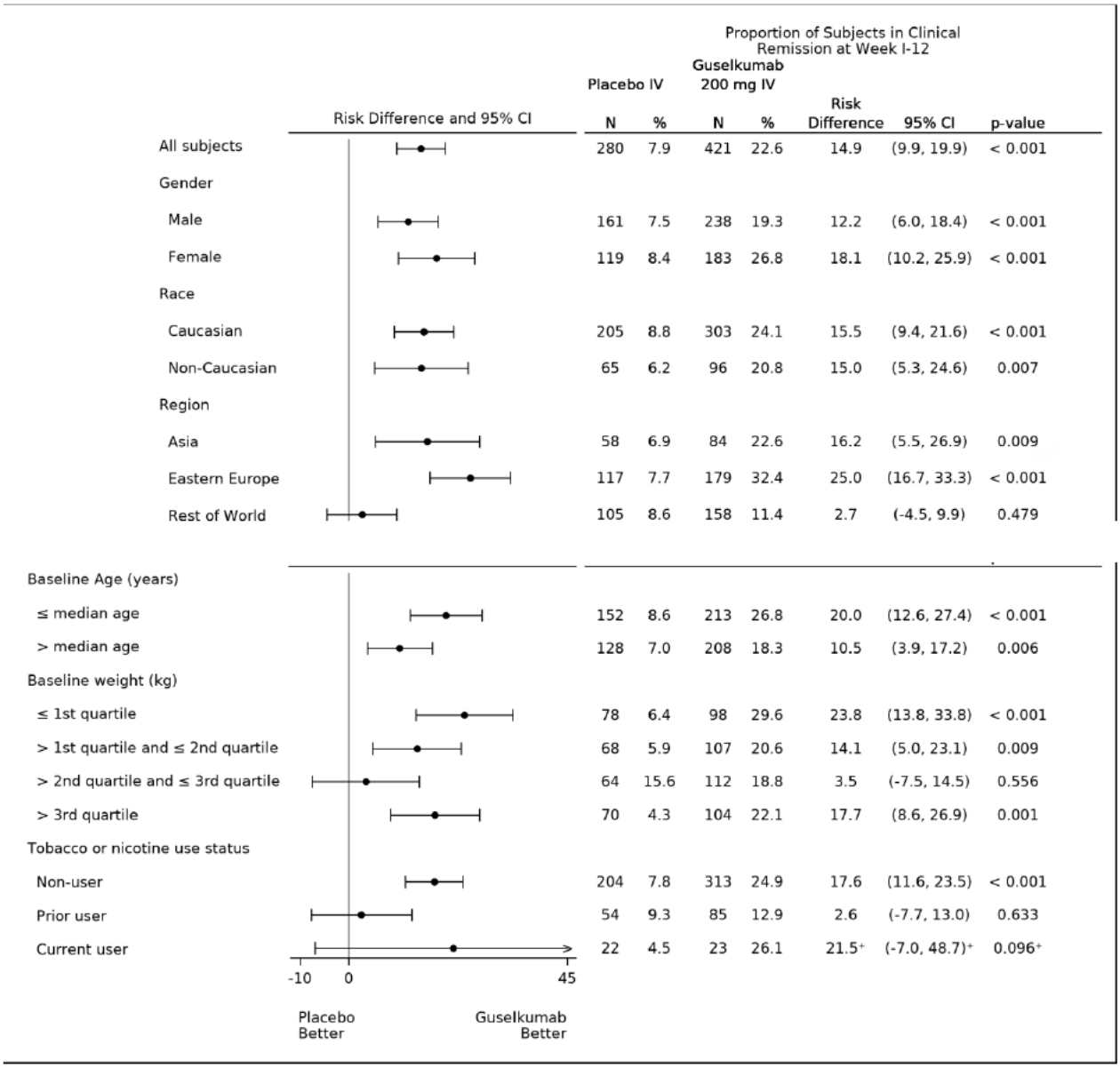
- Clinical remission at Week I-24: 19.4%
- Clinical response at Week I-24: 69.7%
- Symptomatic remission at Week I-24: 57.0%
- Endoscopic healing at Week I-24: 23.0%
- Endoscopic normalization at Week I-24: 12.7%
- Histologic healing at Week I-24: 47.3%
- Histologic remission at Week I-24: 37.6%
- Histologic-endoscopic mucosal healing at Week I-24: 18.8%
- Deep histologic-endoscopic mucosal healing at Week I-24: 11.5%
- Mayo Score at Week I-24: -4.6
- Partial Mayo Score at Week I-24: -3.9

- Modified Mayo Score at Week I-24: -3.3
- Stool frequency subscores at Week I-24: -1.3
- Rectal bleeding subscores at Week I-24: -1.3

### Ancillary analyses

### Subgroup analysis by key subgroups

**Table 20: Primary Endpoint Analysis (Primary Estimand, Subgroup Analysis): Plot of Risk Differences and 95% Confidence Intervals for Clinical Remission at Week I-12 in Guselkumab 200 mg IV Group Versus Placebo IV by Demographic Subgroups; Full Analysis Set (Study CNTO1959UCO3001; IS 2)**




Key: NC=not computable.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
(1) Clinical remission is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
(2) Intercurrent Event (ICE) Strategies: Subjects who had an ostomy or colectomy (ICE 1), a prohibited change in UC medications (ICE 2), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 3)

prior to Week I-12 were considered not to be in clinical remission at Week I-12. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 4) prior to Week I-12, their observed values were used, if available. Subjects who experienced ICE 5 (discontinued study agent due to reasons other than those in ICEs 3 and 4) prior to Week I-12 were considered not to be in clinical remission at Week I-12.
(3) Nonresponder Imputation for Missing Data: After accounting for ICEs, subjects who were missing one or more Mayo subscore pertaining to this endpoint (stool frequency, rectal bleeding, or endoscopy) at Week I-12 were considered not to be in clinical remission.
(4) If the Mantel Fleiss criterion was not satisfied, the Fisher's exact test was used to calculate the p-values, the raw risk difference was calculated based on the observed data, and the confidence intervals were based on the exact confidence limits. Otherwise, the p-values were based on the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No), and the adjusted treatment difference and confidence intervals were based on the Wald statistic with Cochran-Mantel-Haenszel weight. The symbol "+" was attached as a superscript to those p-values, risk difference, and confidence intervals when Mantel Fleiss criterion was not satisfied.

*Subgroup analysis by Baseline ADT failure status*

**Table 21: Key Efficacy Endpoints by Baseline ADT-failure Status (CNTO1959UCO3001 Phase 3 Induction Study 2; Full Analysis Set)**

| | ADT-naïve | | ADT-nonfailure | | ADT-failure | |
|---|---|---|---|---|---|---|
| | Placebo IV | Guselkumab 200 mg IV | Placebo IV | Guselkumab 200 mg IV | Placebo IV | Guselkumab 200 mg IV |
| N | 137 | 202 | 144 | 213 | 136 | 208 |
| Clinical remission at Week I-12 (primary endpoint) | 16 (11.7%) | 64 (31.7%)‡ | 17 (11.8%) | 69 (32.4%)‡ | 5 (3.7%) | 26 (12.5%)† |
| Symptomatic remission at Week I-12 | 36 (26.3%) | 122 (60.4%)‡ | 39 (27.1%) | 130 (61.0%)‡ | 19 (14.0%) | 80 (38.5%)‡ |
| Endoscopic healing at Week I-12 | 23 (16.8%) | 77 (38.1%)‡ | 24 (16.7%) | 82 (38.5%)‡ | 7 (5.1%) | 31 (14.9%)† |
| Clinical response at Week I-12 | 48 (35.0%) | 144 (71.3%)‡ | 51 (35.4%) | 152 (71.4%)‡ | 27 (19.9%) | 107 (51.4%)‡ |
| Symptomatic remission at Week I-4 | 23 (16.8%) | 63 (31.2%)† | 25 (17.4%) | 64 (30.0%)† | 11 (8.1%) | 31 (14.9%) |
| IBDQ remission at Week I-12 | 47 (34.3%) | 126 (62.4%)‡ | 50 (34.7%) | 134 (62.9%)‡ | 33 (24.3%) | 82 (39.4%)† |
| Histologic-endoscopic mucosal healing at Week I-12 | 15 (10.9%) | 66 (32.7%)‡ | 15 (10.4%) | 71 (33.3%)‡ | 6 (4.4%) | 28 (13.5%)† |
| Fatigue response at Week I-12 | 40 (29.2%) | 84 (41.6%)* | 42 (29.2%) | 93 (43.7%)† | 18 (13.2%) | 80 (38.5%)‡ |
| Symptomatic remission at Week I-2 | 17 (12.4%) | 35 (17.3%) | 19 (13.2%) | 35 (16.4%) | 7 (5.1%) | 16 (7.7%) |
| Endoscopic normalization at Week I-12 | 10 (7.3%) | 42 (20.8%)‡ | 11 (7.6%) | 45 (21.1%)‡ | 3 (2.2%) | 18 (8.7%)* |

‡p<0.001; †p<0.01; *p≤0.05. **All p-values are nominal** and are based on the CMH chi-square test.
Note: Includes only participants with a modified Mayo score of 5-9 at baseline.

**Clinical efficacy results in the Week-12 Non-responder subpopulation**

The MAH was asked to provide the Week-24 results for the ADT-failed and the ADT-non failed subgroups on the key clinical efficacy endpoints in the Placebo → Guselkumab 200 mg iv. switched patients and in the Guselkumab 200 mg iv → guselkumab 200 mg sc. switched patients (both subpopulations were nonresponder at Week 12). The MAH was also asked to present these Week 24 results by the following ADT failure categories as a minimum: 0 ADT failed (=ADT nonfailure subgroup), 1 ADT failed, 2 or more ADT failed.

**Figure 20: Summary of Key Efficacy Endpoints at Week I-24 Among Subjects Who Were ADT Non-failure; Week I-12 Clinical Nonresponder Analysis Set (Study CNTO1959UCO3001; Induction 2)**

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|
| Analysis set: Week I-12 Clinical Nonresponder[a] | 165 | 125 |
| Subjects who were ADT non-failure | 76 (46.1%) | 47 (37.6%) |
| Subjects in clinical remission at Week I-24[b1,c,d,e] | 26 (34.2%) | 9 (19.1%) |
| 95% CI for treatment proportion[f] | (23.5%, 44.9%) | (7.9%, 30.4%) |
| Subjects in symptomatic remission at Week I-24[b2,c,d,e] | 52 (68.4%) | 25 (53.2%) |
| 95% CI for treatment proportion[f] | (58.0%, 78.9%) | (38.9%, 67.5%) |
| Subjects with endoscopic healing at Week I-24[b3,c,d,e] | 28 (36.8%) | 10 (21.3%) |
| 95% CI for treatment proportion[f] | (26.0%, 47.7%) | (9.6%, 33.0%) |
| Subjects in clinical response at Week I-24[b4,c,d,e] | 59 (77.6%) | 29 (61.7%) |
| 95% CI for treatment proportion[f] | (68.3%, 87.0%) | (47.8%, 75.6%) |
| Subjects in IBDQ remission at Week I-24[b5,c,d,e] | 50 (65.8%) | 24 (51.1%) |
| 95% CI for treatment proportion[f] | (55.1%, 76.5%) | (36.8%, 65.4%) |
| Subjects with histologic-endoscopic mucosal healing at Week I-24[b6,c,d,e] | 25 (32.9%) | 8 (17.0%) |
| 95% CI for treatment proportion[f] | (22.3%, 43.5%) | (6.3%, 27.8%) |
| Subjects in fatigue response at Week I-24[b7,c,d,e] | 33 (43.4%) | 23 (48.9%) |
| 95% CI for treatment proportion[f] | (32.3%, 54.6%) | (34.6%, 63.2%) |
| Subjects with endoscopic normalization at Week I-24[b8,c,d,e] | 19 (25.0%) | 6 (12.8%) |
| 95% CI for treatment proportion[f] | (15.3%, 34.7%) | (3.2%, 22.3%) |

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|

Key: ADT=advanced therapy; IBDQ=Inflammatory Bowel Disease Questionnaire; PROMIS=Patient-Reported Outcomes Measurement Information System.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
[a] Subjects who were not in clinical response at Week I-12 as determined by IWRS and received treatment from Week I-12.
[b1] Clinical remission is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
[b2] Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.
[b3] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
[b4] Clinical response is defined as a decrease from induction baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.
[b5] IBDQ remission is defined as a total IBDQ score ≥ 170.
[b6] Histologic-endoscopic mucosal healing is defined as achieving a combination of histologic healing and endoscopic healing. Histologic healing is defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system.
[b7] Fatigue response is defined as ≥ 7-point improvement from baseline in the PROMIS Fatigue Short Form 7a.
[b8] Endoscopic normalization is defined as an endoscopy subscore of 0.
[c] Denominator is subjects who were ADT non-failure.
[d] Intercurrent Event (ICE) Strategies: Subjects who had an ostomy or colectomy (ICE 1), a prohibited change in UC medications (ICE 2), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 3) prior to Week I-24 were considered not to have achieved any of the key efficacy endpoints shown at Week I-24. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 4) prior to Week I-24, their observed values were used, if available. Subjects who experienced ICE 5 (discontinued study agent due to reasons other than those in ICEs 3 and 4) prior to Week I-24 were considered not to have achieved any of the key efficacy endpoints shown at Week I-24.
[e] Nonresponder Imputation for Missing Data: After accounting for ICEs, subjects who were missing one or more of the components pertaining to an endpoint at Week I-24 were considered not to have achieved the endpoint. Subjects who had an unevaluable biopsy (i.e., a biopsy that was collected, but could not be assessed due to sample preparation or technical errors) were considered not to have achieved the histology endpoints.
[f] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.

**Table 22: Summary of Key Efficacy Endpoints at Week I-24 Among Subjects Who Were ADT-failure; Week I-12 Clinical Nonresponder Analysis Set (Study CNTO1959UCO3001; Induction 2)**

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|
| Analysis set: Week I-12 Clinical Nonresponder[a] | 165 | 125 |
| Subjects who were ADT-failure | 89 (53.9%) | 78 (62.4%) |
| Subjects in clinical remission at Week I-24[b1,c,d,e] | 6 (6.7%) | 3 (3.8%) |
| 95% CI for treatment proportion[f] | (1.5%, 12.0%) | (0.0%, 8.1%) |
| Subjects in symptomatic remission at Week I-24[b2,c,d,e] | 42 (47.2%) | 26 (33.3%) |
| 95% CI for treatment proportion[f] | (36.8%, 57.6%) | (22.9%, 43.8%) |
| Subjects with endoscopic healing at Week I-24[b3,c,d,e] | 10 (11.2%) | 6 (7.7%) |
| 95% CI for treatment proportion[f] | (4.7%, 17.8%) | (1.8%, 13.6%) |
| Subjects in clinical response at Week I-24[b4,c,d,e] | 56 (62.9%) | 40 (51.3%) |
| 95% CI for treatment proportion[f] | (52.9%, 73.0%) | (40.2%, 62.4%) |
| Subjects in IBDQ remission at Week I-24[b5,c,d,e] | 40 (44.9%) | 30 (38.5%) |
| 95% CI for treatment proportion[f] | (34.6%, 55.3%) | (27.7%, 49.3%) |
| Subjects with histologic-endoscopic mucosal healing at Week I-24[b6,c,d,e] | 6 (6.7%) | 5 (6.4%) |
| 95% CI for treatment proportion[f] | (1.5%, 12.0%) | (1.0%, 11.8%) |
| Subjects in fatigue response at Week I-24[b7,c,d,e] | 33 (37.1%) | 23 (29.5%) |
| 95% CI for treatment proportion[f] | (27.0%, 47.1%) | (19.4%, 39.6%) |
| Subjects with endoscopic normalization at Week I-24[b8,c,d,e] | 2 (2.2%) | 2 (2.6%) |
| 95% CI for treatment proportion[f] | (0.0%, 5.3%) | (0.0%, 6.1%) |

**Table 23: Summary of Key Efficacy Endpoints at Week I-24 Among Subjects Who Were ADT-naive; Week I-12 Clinical Nonresponder Analysis Set (Study CNTO1959UCO3001; Induction 2**

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|
| Analysis set: Week I-12 Clinical Nonresponder[a] | 165 | 125 |
| Subjects who were ADT-naive | 73 (44.2%) | 45 (36.0%) |
| Subjects in clinical remission at Week I-24[b1,c,d,e] | 25 (34.2%) | 9 (20.0%) |
| 95% CI for treatment proportion[f] | (23.4%, 45.1%) | (8.3%, 31.7%) |
| Subjects in symptomatic remission at Week I-24[b2,c,d,e] | 50 (68.5%) | 24 (53.3%) |
| 95% CI for treatment proportion[f] | (57.8%, 79.1%) | (38.8%, 67.9%) |
| Subjects with endoscopic healing at Week I-24[b3,c,d,e] | 27 (37.0%) | 10 (22.2%) |
| 95% CI for treatment proportion[f] | (25.9%, 48.1%) | (10.1%, 34.4%) |
| Subjects in clinical response at Week I-24[b4,c,d,e] | 57 (78.1%) | 28 (62.2%) |
| 95% CI for treatment proportion[f] | (68.6%, 87.6%) | (48.1%, 76.4%) |
| Subjects in IBDQ remission at Week I-24[b5,c,d,e] | 47 (64.4%) | 23 (51.1%) |
| 95% CI for treatment proportion[f] | (53.4%, 75.4%) | (36.5%, 65.7%) |
| Subjects with histologic-endoscopic mucosal healing at Week I-24[b6,c,d,e] | 24 (32.9%) | 8 (17.8%) |
| 95% CI for treatment proportion[f] | (22.1%, 43.7%) | (6.6%, 28.9%) |
| Subjects in fatigue response at Week I-24[b7,c,d,e] | 32 (43.8%) | 21 (46.7%) |
| 95% CI for treatment proportion[f] | (32.5%, 55.2%) | (32.1%, 61.2%) |
| Subjects with endoscopic normalization at Week I-24[b8,c,d,e] | 18 (24.7%) | 6 (13.3%) |
| 95% CI for treatment proportion[f] | (14.8%, 34.5%) | (3.4%, 23.3%) |

**Table 24: Summary of Key Efficacy Endpoints at Week I-24 Among Subjects Who Had Failed One ADT Class; Week I-12 Clinical Non responder Analysis Set (Study CNTO1959UCO3001; Induction 2)**

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|
| Analysis set: Week I-12 Clinical Nonresponder[a] | 165 | 125 |
| Subjects who had failed one ADT class | 45 (27.3%) | 34 (27.2%) |
| Subjects in clinical remission at Week I-24[b1,c,d,e] | 4 (8.9%) | 1 (2.9%) |
| 95% CI for treatment proportion[f] | (0.6%, 17.2%) | (0.0%, 8.6%) |
| Subjects in symptomatic remission at Week I-24[b2,c,d,e] | 23 (51.1%) | 12 (35.3%) |
| 95% CI for treatment proportion[f] | (36.5%, 65.7%) | (19.2%, 51.4%) |
| Subjects with endoscopic healing at Week I-24[b3,c,d,e] | 6 (13.3%) | 3 (8.8%) |
| 95% CI for treatment proportion[f] | (3.4%, 23.3%) | (0.0%, 18.4%) |
| Subjects in clinical response at Week I-24[b4,c,d,e] | 32 (71.1%) | 23 (67.6%) |
| 95% CI for treatment proportion[f] | (57.9%, 84.4%) | (51.9%, 83.4%) |
| Subjects in IBDQ remission at Week I-24[b5,c,d,e] | 22 (48.9%) | 18 (52.9%) |
| 95% CI for treatment proportion[f] | (34.3%, 63.5%) | (36.2%, 69.7%) |
| Subjects with histologic-endoscopic mucosal healing at Week I-24[b6,c,d,e] | 3 (6.7%) | 3 (8.8%) |
| 95% CI for treatment proportion[f] | (0.0%, 14.0%) | (0.0%, 18.4%) |
| Subjects in fatigue response at Week I-24[b7,c,d,e] | 18 (40.0%) | 12 (35.3%) |
| 95% CI for treatment proportion[f] | (25.7%, 54.3%) | (19.2%, 51.4%) |
| Subjects with endoscopic normalization at Week I-24[b8,c,d,e] | 2 (4.4%) | 1 (2.9%) |
| 95% CI for treatment proportion[f] | (0.0%, 10.5%) | (0.0%, 8.6%) |

**Table 25: Summary of Key Efficacy Endpoints at Week I-24 Among Subjects Who Had Failed At Least Two ADT Classes; Week I-12 Clinical Nonresponder Analysis Set (Study CNTO1959UCO3001; Induction 2)**

| | Placebo IV → Guselkumab 200 mg IV | Guselkumab 200 mg IV → Guselkumab 200 mg SC |
|---|---|---|
| Analysis set: Week I-12 Clinical Nonresponder[a] | 165 | 125 |
| Subjects who had failed at least two ADT classes | 44 (26.7%) | 44 (35.2%) |
| Subjects in clinical remission at Week I-24[b1,c,d,e] | 2 (4.5%) | 2 (4.5%) |
| 95% CI for treatment proportion[f] | (0.6%, 15.5%) | (0.6%, 15.5%) |
| Subjects in symptomatic remission at Week I-24[b2,c,d,e] | 19 (43.2%) | 14 (31.8%) |
| 95% CI for treatment proportion[f] | (28.4%, 59.0%) | (18.6%, 47.6%) |
| Subjects with endoscopic healing at Week I-24[b3,c,d,e] | 4 (9.1%) | 3 (6.8%) |
| 95% CI for treatment proportion[f] | (2.5%, 21.7%) | (1.4%, 18.7%) |
| Subjects in clinical response at Week I-24[b4,c,d,e] | 24 (54.5%) | 17 (38.6%) |
| 95% CI for treatment proportion[f] | (38.9%, 69.6%) | (24.4%, 54.5%) |
| Subjects in IBDQ remission at Week I-24[b5,c,d,e] | 18 (40.9%) | 12 (27.3%) |
| 95% CI for treatment proportion[f] | (26.3%, 56.8%) | (15.0%, 42.8%) |
| Subjects with histologic-endoscopic mucosal healing at Week I-24[b6,c,d,e] | 3 (6.8%) | 2 (4.5%) |
| 95% CI for treatment proportion[f] | (1.4%, 18.7%) | (0.6%, 15.5%) |
| Subjects in fatigue response at Week I-24[b7,c,d,e] | 15 (34.1%) | 11 (25.0%) |
| 95% CI for treatment proportion[f] | (20.5%, 49.9%) | (13.2%, 40.3%) |
| Subjects with endoscopic normalization at Week I-24[b8,c,d,e] | 0 | 1 (2.3%) |
| 95% CI for treatment proportion[f] | (0.0%, 8.0%) | (0.1%, 12.0%) |

**Cross-study comparisons - QUASAR IS-1 and IS-2 induction studies**

*Key Clinical Endpoints*

**Table 26: Number of Participants Who Achieved Key Efficacy Endpoints (CNTO1959UCO3001 Induction 1 and Induction 2 Studies; Full Analysis Set)**

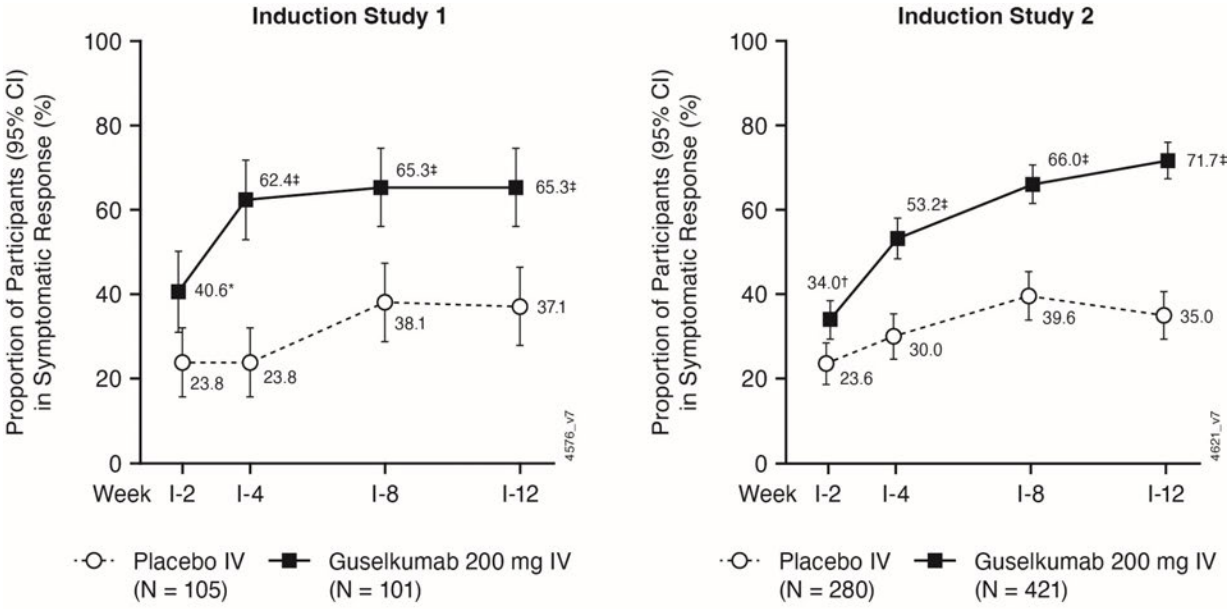
| | Induction Study 1 (Phase 2b) | | Induction Study 2 (Phase 3) | |
|---|---|---|---|---|
| | Placebo IV | Guselkumab 200 mg IV | Placebo IV | Guselkumab 200 mg IV |
| Full Analysis Set | 105 | 101 | 280 | 421 |
| **Phase 3 Primary Endpoint** | | | | |
| Clinical remission at Week I-12 | 10 (9.5%) | 26 (25.7%)† | 22 (7.9%) | 95 (22.6%)‡ |
| **Phase 3 Major Secondary Endpoints** | | | | |
| Symptomatic remission at Week I-12 | 21 (20.0%) | 50 (49.5%)‡ | 58 (20.7%) | 210 (49.9%)‡ |
| Endoscopic healing at Week I-12 | 13 (12.4%) | 31 (30.7%)† | 31 (11.1%) | 113 (26.8%)‡ |
| Clinical response at Week I-12 | 29 (27.6%) | 62 (61.4%)‡ | 78 (27.9%) | 259 (61.5%)‡ |
| Symptomatic remission at Week I-4 | 5 (4.8%) | 18 (17.8%)† | 36 (12.9%) | 95 (22.6%)‡ |
| IBDQ remission at Week I-12 | 28 (26.7%) | 53 (52.5%)‡ | 83 (29.6%) | 216 (51.3%)‡ |
| Histologic-endoscopic mucosal healing at Week I-12 | 9 (8.6%) | 21 (20.8%)* | 21 (7.5%) | 99 (23.5%)‡ |
| Fatigue response at Week I-12 | 31 (29.5%) | 45 (44.6%)* | 60 (21.4%) | 173 (41.1%)‡ |
| Symptomatic remission at Week I-2 | 4 (3.8%) | 10 (9.9%) | 26 (9.3%) | 51 (12.1%) |
| Endoscopic normalization at Week I-12 | 7 (6.7%) | 18 (17.8%)* | 14 (5.0%) | 63 (15.0%)‡ |
| **Other Key Endpoints** | | | | |
| Histologic healing at Week I-12 | 23 (21.9%) | 40 (39.6%)† | 60 (21.4%) | 189 (44.9%)‡ |
| Histologic remission at Week I-12 | 19 (18.1%) | 35 (34.7%)† | 52 (18.6%) | 168 (39.9%)‡ |

‡p<0.001; †p<0.01; *p<0.05. p-values were based on the Cochran-Mantel-Haenszel chi-square test.

Note: Includes only participants with a modified Mayo score of 5 to 9 at induction baseline.

- For IS-1, only the primary endpoint, clinical response at Week I-12 was multiplicity controlled**; all other p-values are nominal**.
- For IS-2, the primary and major secondary endpoints were multiplicity controlled; **p-values reported for endoscopic normalization and other key endpoints at Week I-12 are nominal**.

**Figure 21: Symptomatic Response Over Time Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**

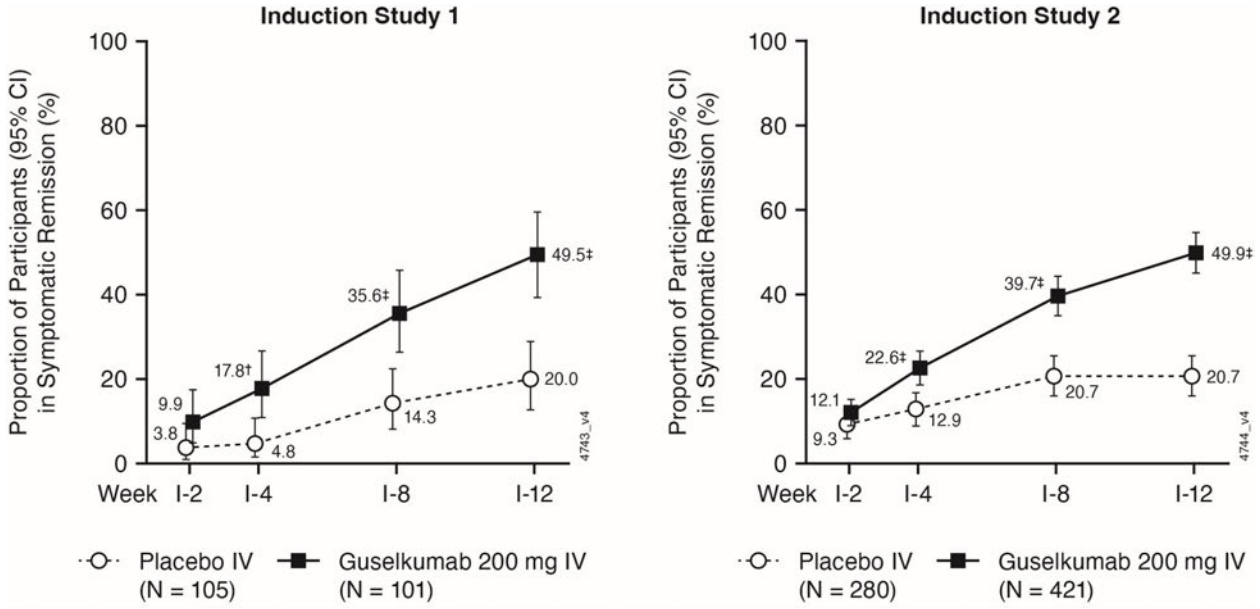



All p-values are nominal: *p<0.05 †p<0.01 ‡p<0.001

Note: Includes only participants with modified Mayo score 5-9 at induction baseline.

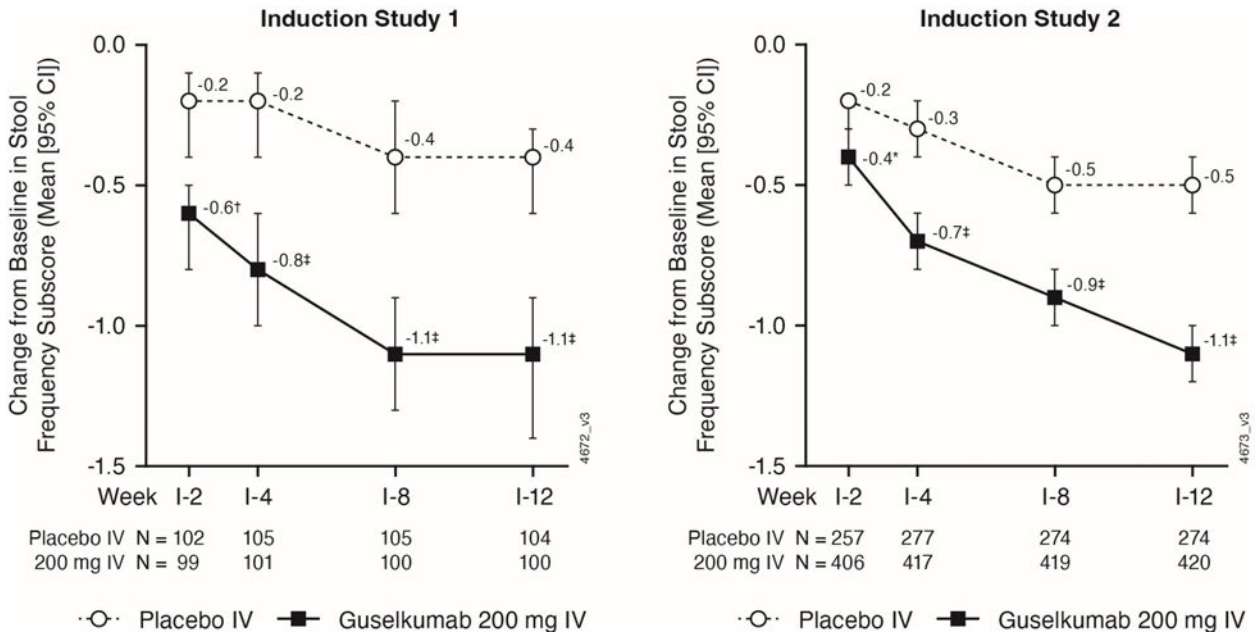
Symptomatic response is defined a decrease from induction baseline in the symptomatic Mayo score by ≥30% and ≥1 point, with either a ≥1-point decrease from induction baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. The symptomatic Mayo score is defined as the sum of the stool frequency and the rectal bleeding subscores.

**Figure 22: Symptomatic Remission Over Time Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**



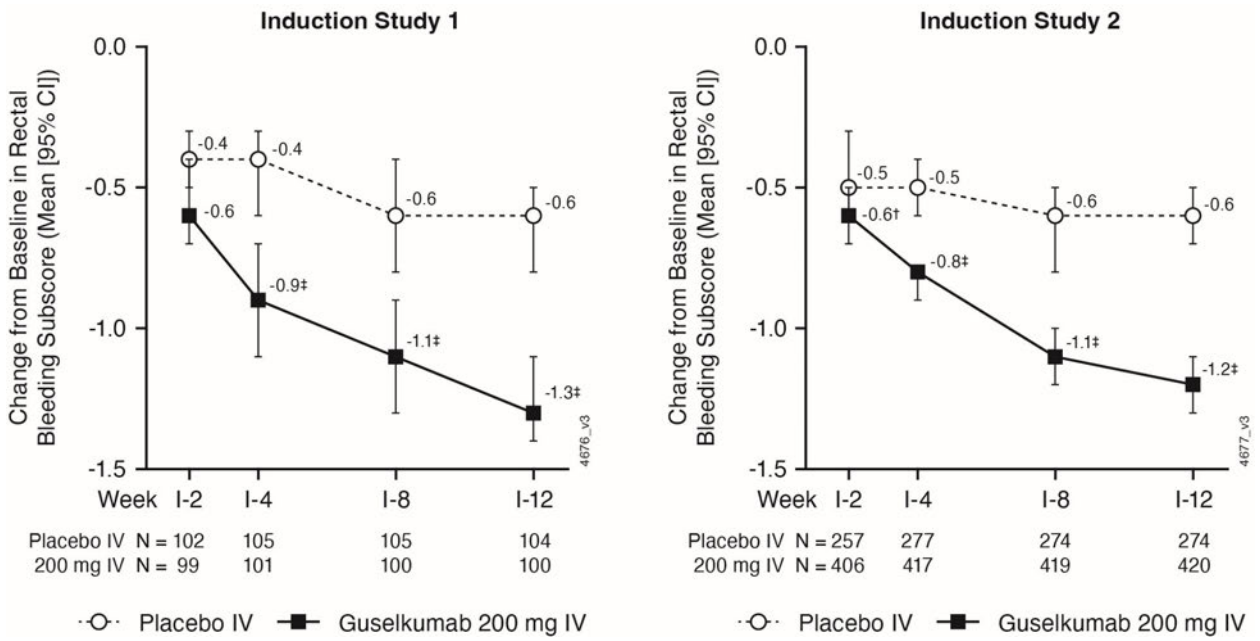

- ‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal except Induction Study 2 at Weeks I-2, I-4, and I-12.
- Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.
- Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

**Figure 23: Change From Baseline in Stool Frequency Subscore Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**



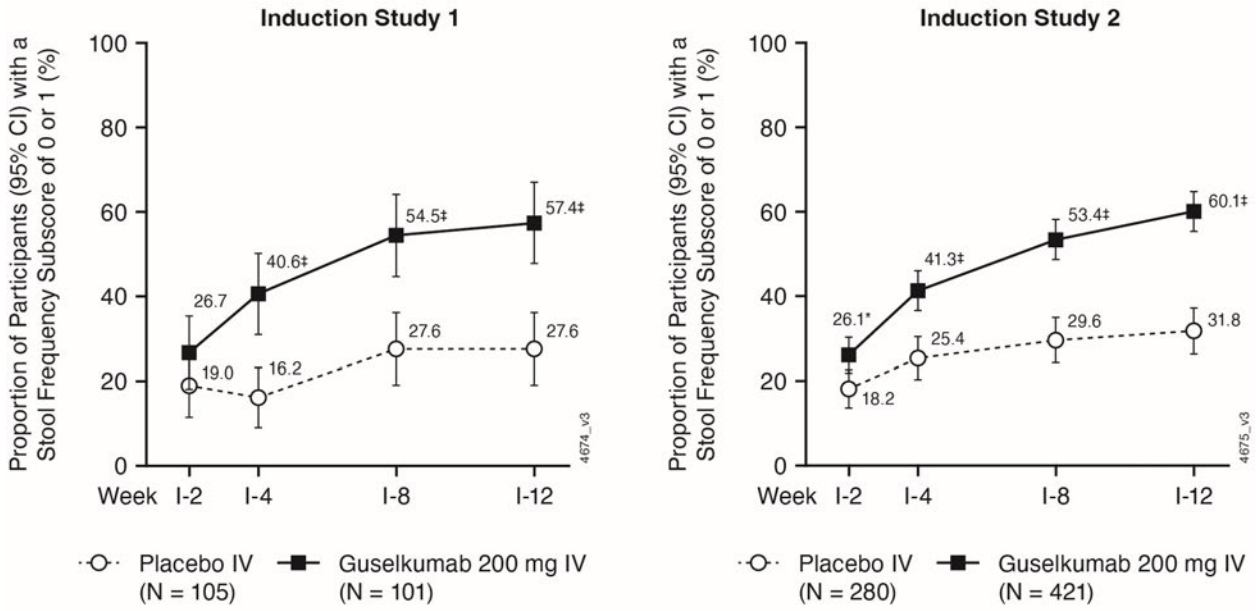

‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal.
Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

**Figure 24: Change From Baseline in Rectal Bleeding Subscore Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**




‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal.
Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

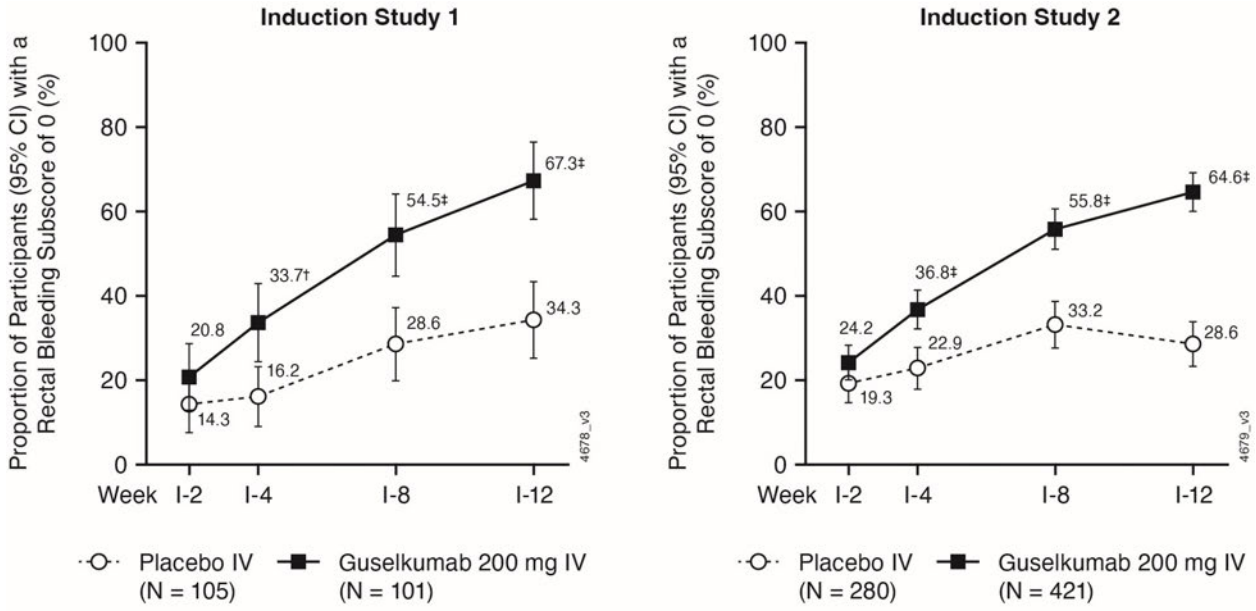
**Figure 25: Proportion of Participants With a Stool Frequency Subscore of 0 or 1 Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**




‡p<0.001 †p<0.01 *p<0.05. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

**Figure 26: Proportion of Participants With a Rectal Bleeding Subscore of 0 Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**



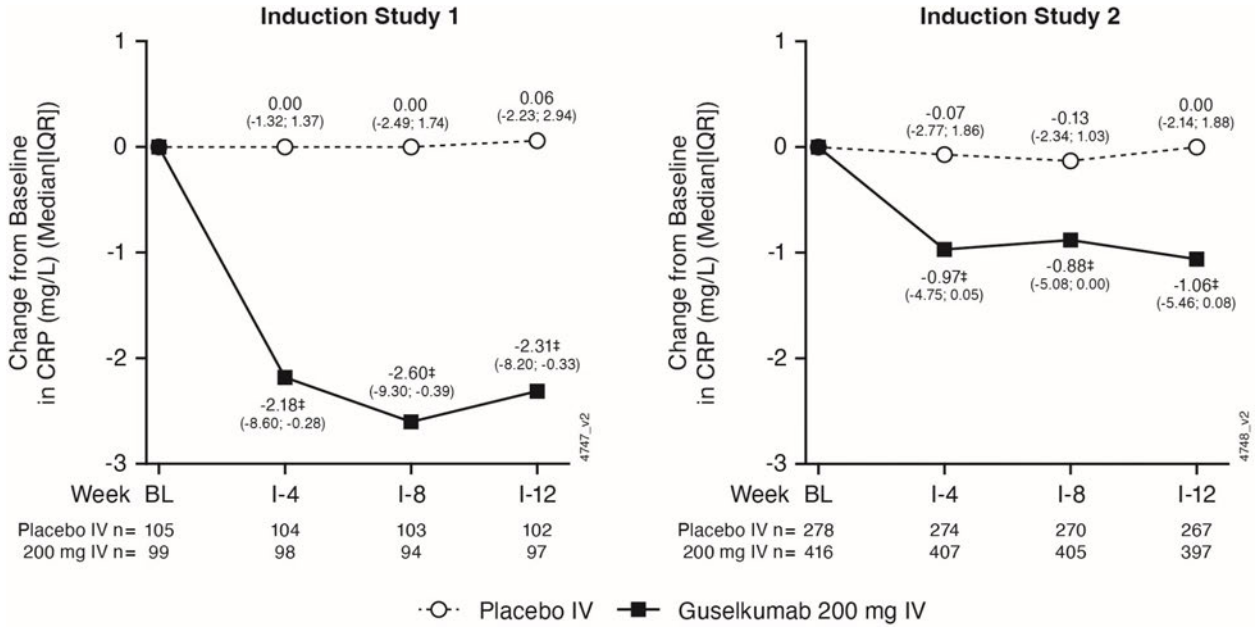

‡p<0.001 †p<0.01 *p<0.05. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

**Inflammatory Biomarkers**

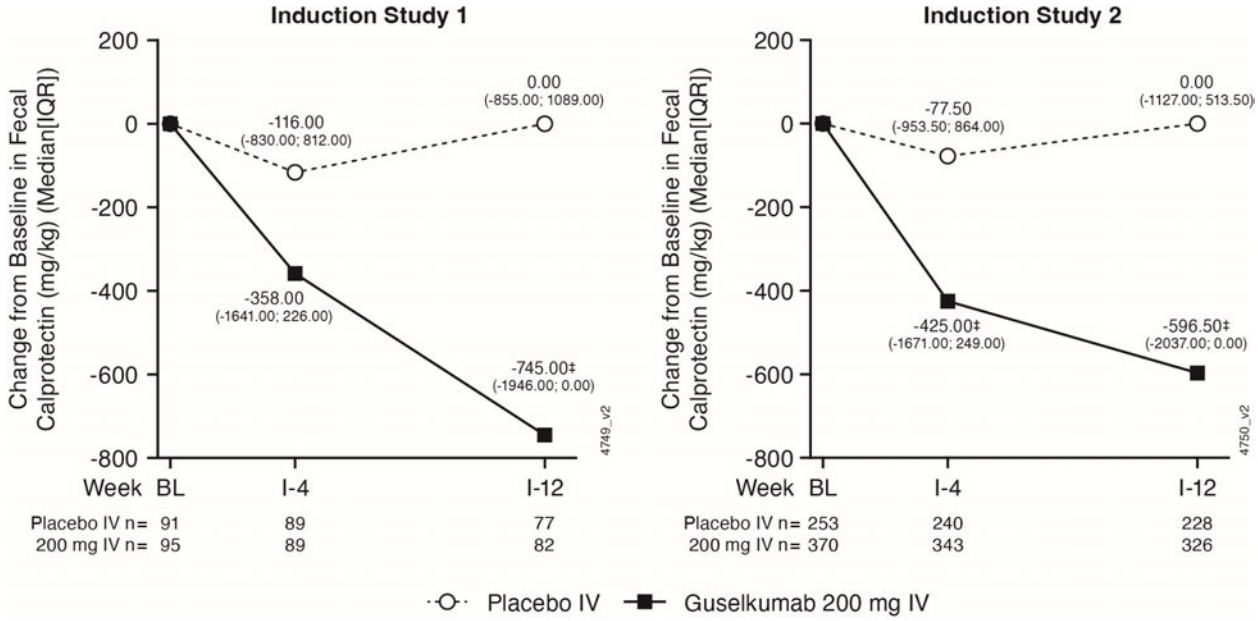
At induction baseline, more than half of the participants in both IS-1 and IS-2 had elevated serum CRP (>3 mg/L; 62.7% and 58.8%, respectively) and fecal calprotectin concentrations (>250 mg/kg; 89.5% and 89.6%, respectively).

**Figure 27: Median Change From Baseline in CRP Concentration (mg/L) Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**




‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal.
Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

**Figure 28: Median Change From Baseline in Fecal Calprotectin Concentration (mg/kg) Through Week I-12 (CNTO1959UCO3001 Induction Study 1 and Induction Study 2; Full Analysis Set)**




‡p<0.001; †p<0.01; *p<0.05. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

### 2.6.5.2.2. Study CNTO1959UCO3001 Maintenance (QUASAR M)

***Methods***

- **Study Participants**

The study population for the Phase 3 Maintenance Study included patients with clinical response at Week 12 or at Week 24 from from IS-1 and IS-2.

- **Treatments**

Randomized participants received 1 of 3 study intervention groups:

- Guselkumab 200 mg SC q4w: Participants received guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44. Participants received 2 injections of 100 mg guselkumab at each visit.
- Guselkumab 100 mg SC q8w: Participants received guselkumab 100 mg SC q8w starting at Week M-4 through Week M-44. To maintain the blind, participants received 1 placebo SC injection + 1 injection of 100 mg guselkumab or 2 placebo SC injections at alternate visits.
- Placebo: Participants received placebo SC q4w starting at Week M-0 through Week M-44.

To maintain the blind, participants received 2 placebo injections at each visit.

In addition, guselkumab induction 24-week responders and induction placebo responders at Week I-12 from IS-1 or IS-2 entered the Maintenance Study but were not randomized. Participants remained on their assigned study intervention through Week M-44.

During the Maintenance Study, participants in clinical flare between Week M-4 and Week M-32 (inclusive) underwent an endoscopy to evaluate for loss of clinical response based on the modified Mayo score. Once loss of clinical response was confirmed, the participant was eligible for a blinded dose adjustment.

A participant who met the criteria of clinical flare on more than 1 occasion did not undergo a second evaluation for the loss of clinical response and was discontinued from study intervention administration.

*Dose Adjustment*

Participants who were randomized in the Maintenance Study and met predefined criteria for loss of clinical response were eligible to receive a single blinded dose adjustment to guselkumab 200 mg SC q4w (ie, guselkumab 100 mg SC q8w → guselkumab 200 mg SC q4w, or placebo SC → guselkumab 200 mg SC q4w), beginning at a scheduled visit between Week M-8 and Week M-32. Note that participants randomized to guselkumab 200 mg SC q4w received a sham dose adjustment (ie, 200 mg SC q4w → 200 mg SC q4w).

Non-randomized participants were not eligible for dose adjustment.

*Concomitant and rescue therapies*

For participants who were receiving oral corticosteroids on entry in the Maintenance Study, the investigator was to begin tapering the daily dose of corticosteroids at Week M-0. Tapering of the daily dose of corticosteroids was allowed to be paused for participants who met clinical flare criteria.

Other UC-specific medical therapies (ie, oral 5-ASA compounds, 6-MP, AZA, or MTX) were to be maintained at stable doses through Week M-44 (without initiation or increase in dose) unless investigator judgment required that the therapy be discontinued, or the dose be reduced because of toxicity or medical necessity.

- **Objectives**

The primary efficacy objective of the QUASAR maintenance study was to evaluate the efficacy of maintenance regimens of guselkumab. The primary hypothesis is that guselkumab maintenance

therapy is superior to placebo in achieving clinical remission at Week M-44 in participants with moderately to severely active UC who were induced into clinical response with IV guselkumab.

Secondary efficacy objectives:

- To evaluate the impact of guselkumab on health-related quality of life (HRQoL) and health economics outcome measures.
- To evaluate the Pharmacokinetics (PK), immunogenicity, and Pharmacodynamics (PD) of guselkumab therapy, including changes in CRP and faecal calprotectin.

- **Outcomes/endpoints**

Primary outcome was Clinical remission at Week M-44, major Secondary Endpoints were as follows:

- Symptomatic remission at Week M-44
- Endoscopic healing at Week M-44
- Corticosteroid-free (ie, not requiring any treatment with corticosteroids for at least 8 weeks prior) clinical remission at Week M-44
- Maintenance of clinical response at Week M-44
- Histologic-endoscopic mucosal healing at Week M-44
- IBDQ remission at Week M-44
- Fatigue response at Week M-44
- Clinical remission at Week M-44 among the participants who had achieved clinical remission at maintenance baseline (ie, maintenance of clinical remission at M-44)
- Endoscopic normalization at Week M-44

- **Sample size**

The primary analysis population for the Maintenance Study consisted of 568 participants with a modified Mayo score of 5 to 9 at induction baseline who were randomized and treated in the Maintenance Study: 190 participants in the guselkumab 200 mg SC q4w group, 188 in the guselkumab 100 mg SC q8w group, and 190 in the placebo group.

- **Randomisation and Blinding (masking)**

The following populations were randomized in a 1:1:1 ratio to guselkumab 200 mg, SC q4w, guselkumab 100 mg SC q8w, or placebo SC:

- Guselkumab clinical responders at Week I-12
- Placebo IV → guselkumab clinical responders at Week I-24

Participants were allocated to an intervention group using permuted block randomization stratified by clinical remission status at maintenance baseline (Yes/No), concomitant use of corticosteroids at maintenance baseline (Yes/No), and induction treatment (guselkumab 400 mg IV, guselkumab 200 mg IV, and placebo IV → guselkumab 200 mg IV).

Patient populations entered the Maintenance Study, but were not randomized:

- Induction placebo responders at Week I-12
- Guselkumab induction 24-week responders

Blinding measures were the same within the QUASAR programme and are described at Study IS-1.

- **Statistical methods**

**Efficacy Analysis sets**

- Enrolled Analysis Set: all participants who are assigned to an intervention group in this maintenance study, including both randomized and nonrandomized participants.
- Full Analysis Set (FAS): all participants with a modified Mayo score of 5 to 9 who receive at least 1 (partial or complete) dose of study intervention in this Maintenance Study, including both randomized and nonrandomized.
- Randomized Analysis Set: all participants who are randomized in the study (regardless of modified Mayo score).
- Randomized (Modified Mayo 5-9) Analysis Set: all participants who were randomized in the study with a modified Mayo score of 5 to 9.
- Nonrandomized Full Analysis Set: all the participants with a modified Mayo score of 5 to 9 who enter this Maintenance Study but are not randomized (i.e., Guselkumab 24-week clinical responders, and Placebo responders at Week I-12 from Induction Study 1 or Induction Study 2) and receive at least 1 (partial or complete) dose of study intervention in this Maintenance Study.
- Efficacy All Randomized and Treated Analysis Set: all participants (regardless of modified Mayo score) who are randomized (i.e., Guselkumab clinical responders at Week I-12 and Placebo crossover responders at Week I-24 in an Induction Study) in this Maintenance Study and receive at least 1 (partial or complete) dose of study intervention in this Maintenance Study.
- Efficacy All Non randomized and Treated Analysis Set: all the participants (regardless of modified Mayo score) who enter this Maintenance Study but are not randomized (i.e., Guselkumab 24-week clinical responders, and Placebo responders at Week I-12 from Induction Study 1 or Induction Study 2) and receive at least 1 (partial or complete) dose of study intervention in this Maintenance Study.
- Dose Adjustment Analysis Set: all the participants in the Randomized Full Analysis Set who had a dose adjustment.

**Statistical analyses**

Statistical analysis methods were the same as in the QUASAR IS-2 study.

*Planned subgroup analyses*

The same subgroups were applied as in the Phase 3 induction study (QUASAR – IS 2). For subgroup analyses, the analysis sets are the individual subgroups of the Randomized Full Analysis Set. For each of these subgroups, the rate (risk) difference of each guselkumab group vs placebo and the associated 95% confidence interval were to be provided. The rate (risk) difference and confidence intervals will be provided based on the Cochran-Mantel-Haenszel weight that includes factors for clinical remission status at maintenance baseline (Yes/No), and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover to guselkumab 200 mg). The main estimand for the major secondary endpoints will be used for these subgroup analyses and the missing data rule (i.e., missing values will be imputed as nonresponder) used for the secondary estimands will be applied.

*Sample size determination*

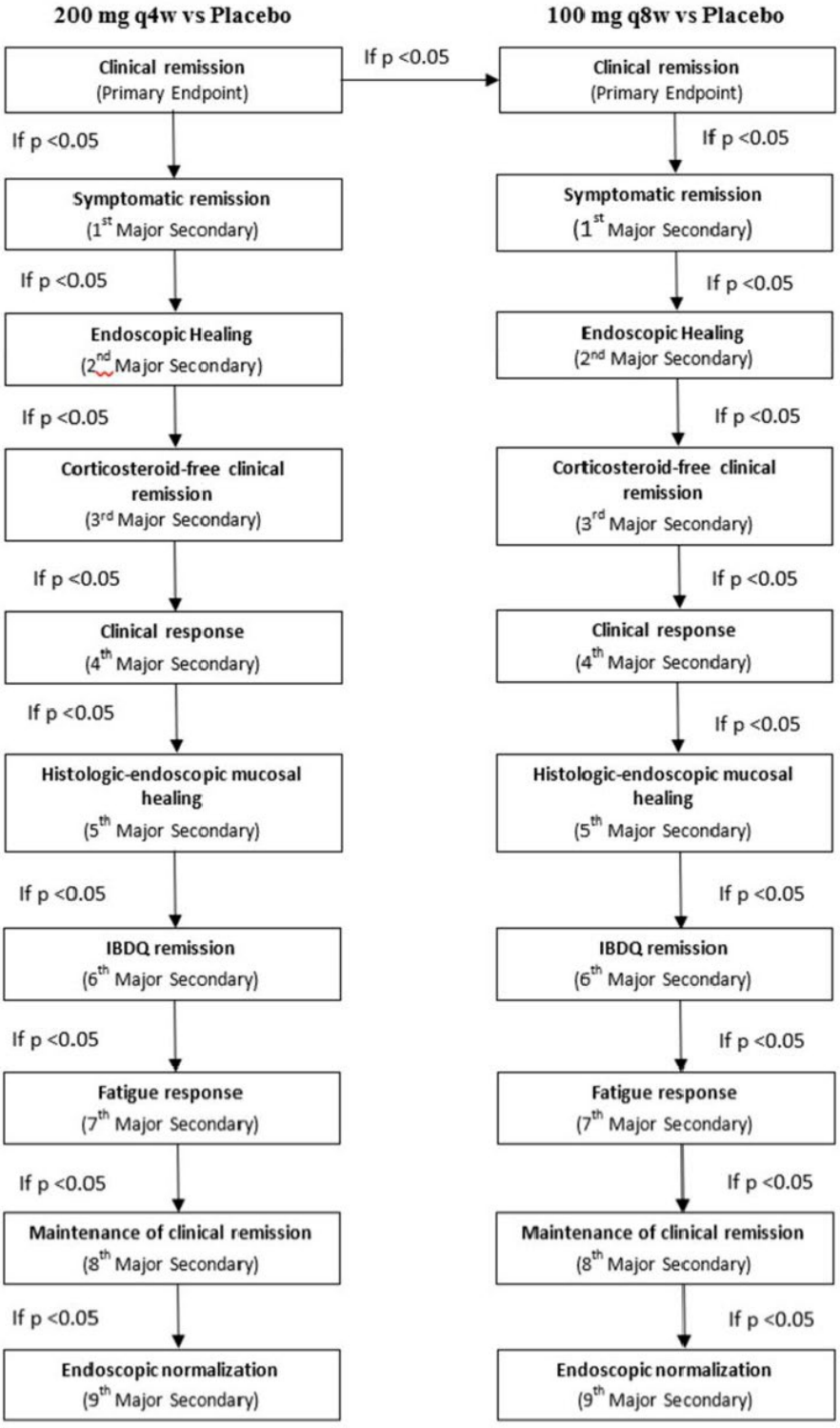
The assumptions for the sample size calculations were based on data from the Phase 3 ustekinumab CNTO1275UCO3001 study, where proportions of participants in clinical remission at Week 44 were 26.3% and 44.9% for placebo and ustekinumab 90 mg SC q8w, respectively, for a treatment difference of 18.6%. Based on these data, the clinical remission at Week M-44 rates are assumed to be 25% for placebo and 45% for each of the guselkumab doses. Given these assumptions, 118 participants in each group (354 participants in total) will provide statistical power of 90% at a significance level of 0.05 (2 sided) for the primary endpoint.

Based on the assumptions in Induction Study 1, the clinical response rate to guselkumab IV induction is expected to be 60%, thus the 2 induction studies will result in approximately 484 participants with a modified Mayo score of 5 to 9 in the primary population of the Maintenance Study. The expected enrollment in the primary population of the Maintenance Study is 484 participants, which is over the required sample size of 354. The targeted number was increased because the maintenance study is intended to power at least 90% for the majority of the major secondary endpoints based on the primary population.

*Error probabilities, adjustment for multiplicity and interim analyses*

Type I error control in countries outside the United States (global testing procedure, including the EU): A hierarchical testing procedure as shown in Figure 29 was employed to control the overall Type 1 error rate over the 9 major secondary efficacy analyses at the (2-sided) 0.05 significance level within a guselkumab dose group, for the doses that test positive for the primary endpoint.

**Figure 29: Multiplicity testing hierarchy (CNTO1959UCO3001 Phase 3 Maintenance Study)**



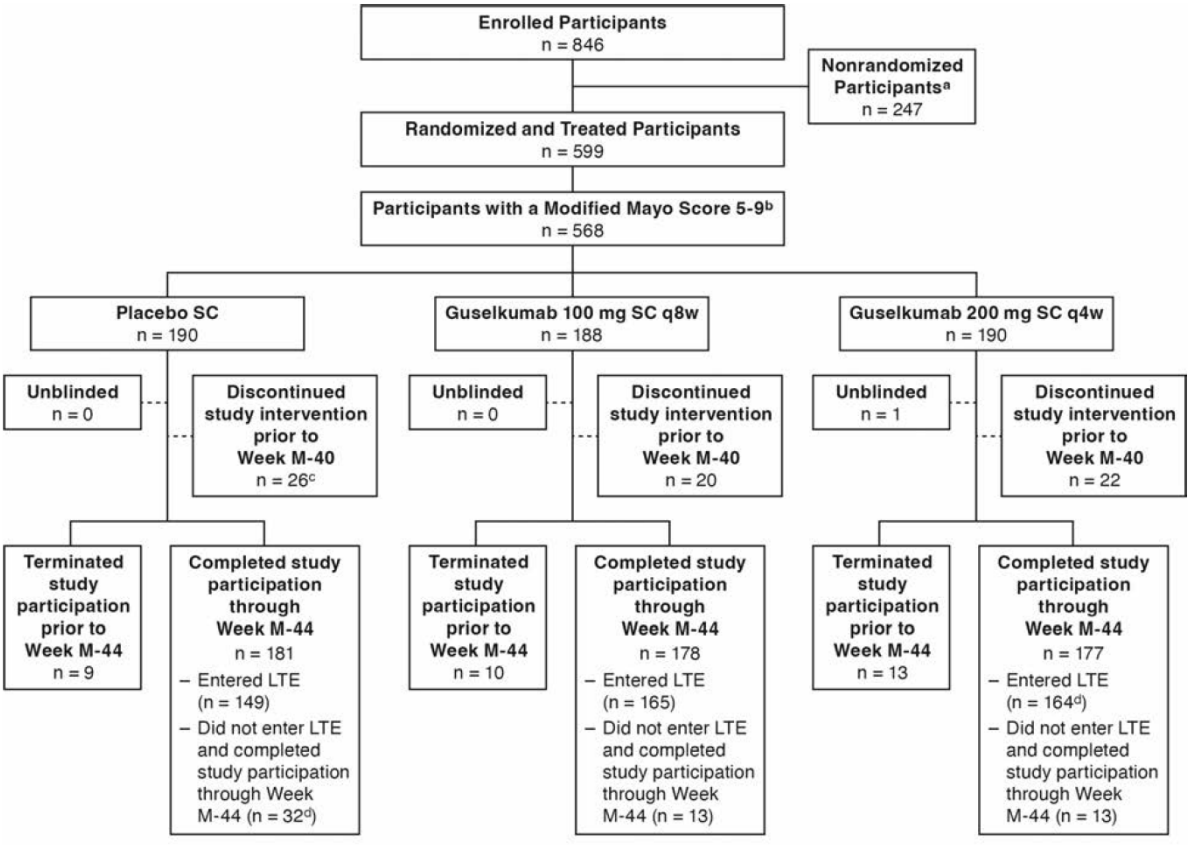

*Changes from protocol-specified analyses*

Amendment of the SAP of the QUASAR studies was dated to 9 September 2021. The significant updates were to accomodate the regulatory query of the inclusion of UC patients with modified Mayo scores between 5 and 9 (both inclusive) instead of the original range of 4-9 and to remove Region as a stratification variable in all efficacy analyses.

***Results***

- **Participant flow**

**Figure 30: Participant flow – QUASAR 3 Maintenance study**




- **Recruitment**

QUASAR Maintenance study initiated on 26 September 2019. Data Cutoff Date for this submission was 19 September 2023. The study is ongoing.

- **Conduct of the study**

Protocol amendment and Major Protocol Deviation were presented in the QUASAR IS-2 induction study section.

- **Baseline data**

**Table 27: Summary of Demographics and Induction Baseline Characteristics (CNTO1959UCO3001 Phase 3 Maintenance Study; Full Analysis Set**

| | Randomized Participants | | | | | Nonrandomized Participants | | |
|---|---|---|---|---|---|---|---|---|
| | Induction Guselkumab IV Responders | | | | | | | |
| | | Guselkumab | | | | Induction Placebo IV Responders | Induction Guselkumab 24-week Responders[c] | |
| Analysis set: Full | Placebo SC[a] 190 | 100 mg SC q8w 188 | 200 mg SC q4w 190 | Combined 378 | Total 568 | Placebo SC[b] 114 | Guselkumab 200 mg SC q4w 123 | Overall Total 805 |
| Age (years) | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 41.2 (13.58) | 40.3 (13.00) | 40.6 (14.66) | 40.4 (13.84) | 40.7 (13.75) | 40.0 (12.70) | 41.5 (14.27) | 40.7 (13.68) |
| Median | 39.5 | 39.0 | 39.0 | 39.0 | 39.0 | 39.0 | 41.0 | 39.0 |
| Range | (18; 76) | (18; 79) | (18; 75) | (18; 79) | (18; 79) | (19; 74) | (18; 74) | (18; 79) |
| IQ range | (31.0; 49.0) | (32.0; 47.0) | (28.0; 53.0) | (30.0; 50.0) | (30.0; 49.0) | (31.0; 48.0) | (30.0; 53.0) | (30.0; 50.0) |
| Age < 65 years | 178 (93.7%) | 176 (93.6%) | 179 (94.2%) | 355 (93.9%) | 533 (93.8%) | 109 (95.6%) | 115 (93.5%) | 757 (94.0%) |
| Age ≥ 65 years | 12 (6.3%) | 12 (6.4%) | 11 (5.8%) | 23 (6.1%) | 35 (6.2%) | 5 (4.4%) | 8 (6.5%) | 48 (6.0%) |
| Sex | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Female | 81 (42.6%) | 86 (45.7%) | 90 (47.4%) | 176 (46.6%) | 257 (45.2%) | 53 (46.5%) | 50 (40.7%) | 360 (44.7%) |
| Male | 109 (57.4%) | 102 (54.3%) | 100 (52.6%) | 202 (53.4%) | 311 (54.8%) | 61 (53.5%) | 73 (59.3%) | 445 (55.3%) |
| Undifferentiated | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Region | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Asia | 30 (15.8%) | 36 (19.1%) | 42 (22.1%) | 78 (20.6%) | 108 (19.0%) | 25 (21.9%) | 32 (26.0%) | 165 (20.5%) |
| Eastern Europe | 102 (53.7%) | 85 (45.2%) | 88 (46.3%) | 173 (45.8%) | 275 (48.4%) | 50 (43.9%) | 55 (44.7%) | 380 (47.2%) |
| Rest of World | 58 (30.5%) | 67 (35.6%) | 60 (31.6%) | 127 (33.6%) | 185 (32.6%) | 39 (34.2%) | 36 (29.3%) | 260 (32.3%) |
| Latin America | 7 (3.7%) | 8 (4.3%) | 10 (5.3%) | 18 (4.8%) | 25 (4.4%) | 6 (5.3%) | 3 (2.4%) | 34 (4.2%) |
| North America | 9 (4.7%) | 9 (4.8%) | 11 (5.8%) | 20 (5.3%) | 29 (5.1%) | 7 (6.1%) | 5 (4.1%) | 41 (5.1%) |
| Western Europe | 31 (16.3%) | 35 (18.6%) | 25 (13.2%) | 60 (15.9%) | 91 (16.0%) | 16 (14.0%) | 14 (11.4%) | 121 (15.0%) |
| Other[d] | 11 (5.8%) | 15 (8.0%) | 14 (7.4%) | 29 (7.7%) | 40 (7.0%) | 10 (8.8%) | 14 (11.4%) | 64 (8.0%) |
| Race | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 34 (17.9%) | 38 (20.2%) | 44 (23.2%) | 82 (21.7%) | 116 (20.4%) | 25 (21.9%) | 32 (26.0%) | 173 (21.5%) |
| Black or African American | 2 (1.1%) | 2 (1.1%) | 2 (1.1%) | 4 (1.1%) | 6 (1.1%) | 1 (0.9%) | 1 (0.8%) | 8 (1.0%) |
| Native Hawaiian or Other Pacific Islander | 1 (0.5%) | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 | 1 (0.1%) |
| White | 142 (74.7%) | 139 (73.9%) | 135 (71.1%) | 274 (72.5%) | 416 (73.2%) | 86 (75.4%) | 84 (68.3%) | 586 (72.8%) |
| Multiple | 1 (0.5%) | 0 | 0 | 0 | 1 (0.2%) | 0 | 1 (0.8%) | 2 (0.2%) |
| Not Reported | 10 (5.3%) | 9 (4.8%) | 9 (4.7%) | 18 (4.8%) | 28 (4.9%) | 2 (1.8%) | 5 (4.1%) | 35 (4.3%) |
| Ethnicity | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Hispanic or Latino | 7 (3.7%) | 10 (5.3%) | 11 (5.8%) | 21 (5.6%) | 28 (4.9%) | 10 (8.8%) | 7 (5.7%) | 45 (5.6%) |
| Not Hispanic or Latino | 173 (91.1%) | 163 (86.7%) | 168 (88.4%) | 331 (87.6%) | 504 (88.7%) | 101 (88.6%) | 107 (87.0%) | 712 (88.4%) |
| Not Reported | 10 (5.3%) | 15 (8.0%) | 11 (5.8%) | 26 (6.9%) | 36 (6.3%) | 3 (2.6%) | 9 (7.3%) | 48 (6.0%) |
| Weight (kg) | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 73.56 (16.997) | 70.68 (16.757) | 70.94 (16.624) | 70.81 (16.669) | 71.73 (16.815) | 70.36 (16.645) | 71.68 (17.449) | 71.53 (16.875) |
| Median | 72.00 | 68.75 | 69.25 | 69.00 | 70.00 | 69.10 | 71.50 | 70.00 |
| Range | (43.2; 126.0) | (40.0; 116.0) | (44.4; 121.6) | (40.0; 121.6) | (40.0; 126.0) | (43.4; 115.0) | (40.9; 121.6) | (40.0; 126.0) |
| IQ range | (61.30; 83.80) | (58.20; 83.50) | (57.50; 81.80) | (58.00; 82.10) | (59.00; 83.00) | (56.00; 82.00) | (57.00; 83.00) | (58.30; 83.00) |

Key: IQ=interquartile; SD=standard deviation.
Note: Includes only participants with modified Mayo score 5-9 at induction baseline.
Note: Participants were presented in the treatment group assigned at Week M-0.
a Participants who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
b Participants who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.
c Participants who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab from Week I-12.
d Includes countries Australia, Israel, Jordan and New Zealand.

**Table 28: Summary of Maintenance Baseline disease Characteristics (CNTO1959UCO3001 Phase 3 Maintenance Study; Full Analysis Set**

| | Randomized Participants | | | | | Nonrandomized Participants | | |
|---|---|---|---|---|---|---|---|---|
| | Induction Guselkumab IV Responders | | | | | Induction Placebo IV Responders | Induction Guselkumab 24-week Responders[c] | |
| | | Guselkumab | | | | | Guselkumab 200 mg SC q4w | |
| | Placebo SC[a] | 100 mg SC q8w | 200 mg SC q4w | Combined | Total | Placebo SC[b] | | Overall Total |
| Analysis set: Full | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mayo score | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 3.3 (2.01) | 3.2 (1.91) | 3.2 (1.85) | 3.2 (1.88) | 3.2 (1.92) | 3.8 (2.08) | 4.3 (1.81) | 3.5 (1.97) |
| Median | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 4.0 | 5.0 | 4.0 |
| Range | (0; 8) | (0; 7) | (0; 8) | (0; 8) | (0; 8) | (0; 8) | (0; 9) | (0; 9) |
| IQ range | (2.0; 5.0) | (2.0; 5.0) | (2.0; 5.0) | (2.0; 5.0) | (2.0; 5.0) | (2.0; 5.0) | (3.0; 6.0) | (2.0; 5.0) |
| Modified Mayo score | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 2.5 (1.57) | 2.6 (1.51) | 2.5 (1.50) | 2.5 (1.51) | 2.5 (1.53) | 2.9 (1.56) | 3.4 (1.41) | 2.7 (1.55) |
| Median | 2.0 | 2.0 | 3.0 | 2.0 | 2.0 | 3.0 | 4.0 | 3.0 |
| Range | (0; 6) | (0; 6) | (0; 6) | (0; 6) | (0; 6) | (0; 6) | (0; 7) | (0; 7) |
| IQ range | (1.0; 4.0) | (1.0; 4.0) | (1.0; 4.0) | (1.0; 4.0) | (1.0; 4.0) | (2.0; 4.0) | (3.0; 4.0) | (2.0; 4.0) |
| Partial Mayo score | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 1.7 (1.34) | 1.6 (1.18) | 1.6 (1.19) | 1.6 (1.18) | 1.6 (1.24) | 2.1 (1.37) | 2.2 (1.35) | 1.8 (1.29) |
| Median | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Range | (0; 5) | (0; 5) | (0; 5) | (0; 5) | (0; 5) | (0; 5) | (0; 6) | (0; 6) |
| IQ range | (1.0; 3.0) | (1.0; 2.0) | (1.0; 2.0) | (1.0; 2.0) | (1.0; 2.0) | (1.0; 3.0) | (1.0; 3.0) | (1.0; 3.0) |
| Endoscopic healing[d] | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Yes | 68 (35.8%) | 75 (39.9%) | 79 (41.6%) | 154 (40.7%) | 222 (39.1%) | 39 (34.2%) | 29 (23.6%) | 290 (36.0%) |
| No | 122 (64.2%) | 113 (60.1%) | 111 (58.4%) | 224 (59.3%) | 346 (60.9%) | 75 (65.8%) | 94 (76.4%) | 515 (64.0%) |
| Endoscopic normalization[e] | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Yes | 39 (20.5%) | 41 (21.8%) | 47 (24.7%) | 88 (23.3%) | 127 (22.4%) | 21 (18.4%) | 12 (9.8%) | 160 (19.9%) |
| No | 151 (79.5%) | 147 (78.2%) | 143 (75.3%) | 290 (76.7%) | 441 (77.6%) | 93 (81.6%) | 111 (90.2%) | 645 (80.1%) |
| Clinical remission[f] | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Yes | 59 (31.1%) | 66 (35.1%) | 69 (36.3%) | 135 (35.7%) | 194 (34.2%) | 33 (28.9%) | 20 (16.3%) | 247 (30.7%) |
| No | 131 (68.9%) | 122 (64.9%) | 121 (63.7%) | 243 (64.3%) | 374 (65.8%) | 81 (71.1%) | 103 (83.7%) | 558 (69.3%) |
| IBDQ remission[g] | | | | | | | | |
| N | 188 | 188 | 189 | 377 | 565 | 112 | 123 | 800 |
| Yes | 142 (75.5%) | 134 (71.3%) | 128 (67.7%) | 262 (69.5%) | 404 (71.5%) | 66 (58.9%) | 67 (54.5%) | 537 (67.1%) |
| No | 46 (24.5%) | 54 (28.7%) | 61 (32.3%) | 115 (30.5%) | 161 (28.5%) | 46 (41.1%) | 56 (45.5%) | 263 (32.9%) |
| CRP (mg/L) | | | | | | | | |
| N | 190 | 188 | 190 | 378 | 568 | 114 | 123 | 805 |
| Mean (SD) | 3.5 (5.13) | 4.6 (11.19) | 3.4 (6.61) | 4.0 (9.18) | 3.8 (8.05) | 4.6 (7.97) | 4.3 (5.64) | 4.0 (7.72) |
| Median | 1.5 | 1.4 | 1.4 | 1.4 | 1.5 | 1.6 | 2.0 | 1.6 |
| Range | (0; 32) | (0; 116) | (0; 71) | (0; 116) | (0; 116) | (0; 50) | (0; 32) | (0; 116) |
| IQ range | (0.6; 4.0) | (0.4; 4.0) | (0.6; 3.4) | (0.5; 3.7) | (0.6; 3.8) | (0.7; 5.2) | (0.9; 6.2) | (0.6; 4.2) |
| Abnormal CRP (> 3 mg/L) | 63 (33.2%) | 63 (33.5%) | 56 (29.5%) | 119 (31.5%) | 182 (32.0%) | 42 (36.8%) | 50 (40.7%) | 274 (34.0%) |
| Fecal calprotectin (mg/kg) | | | | | | | | |
| N | 188 | 185 | 187 | 372 | 560 | 113 | 122 | 795 |
| Mean (SD) | 1143.2 (2683.43) | 1292.3 (2953.34) | 942.4 (1577.16) | 1116.4 (2367.19) | 1125.4 (2475.49) | 1078.0 (1554.96) | 1244.4 (2315.56) | 1136.9 (2339.84) |
| Median | 306.5 | 308.0 | 281.0 | 301.5 | 303.5 | 488.0 | 530.5 | 358.0 |
| Range | (15; 19291) | (15; 27538) | (15; 10708) | (15; 27538) | (15; 27538) | (15; 11027) | (15; 18934) | (15; 27538) |
| IQ range | (82.5; 1077.0) | (71.0; 1310.0) | (89.0; 1233.0) | (78.0; 1282.0) | (79.5; 1194.0) | (91.0; 1488.0) | (186.0; 1335.0) | (88.0; 1273.0) |
| Abnormal fecal calprotectin (> 250 mg/kg) | 102 (54.3%) | 101 (54.6%) | 97 (51.9%) | 198 (53.2%) | 300 (53.6%) | 68 (60.2%) | 79 (64.8%) | 447 (56.2%) |
| Fecal calprotectin > 150 mg/kg | 121 (64.4%) | 116 (62.7%) | 119 (63.6%) | 235 (63.2%) | 356 (63.6%) | 78 (69.0%) | 95 (77.9%) | 529 (66.5%) |

Note: Includes only participants with modified Mayo score 5-9 at induction baseline.
Note: Participants were presented in the treatment group assigned at Week M-0.
a Participants who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
b Participants who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.
c Participants who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab
from Week I-12.
d Endoscopic healing is defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

e Endoscopic normalization is defined as an endoscopy subscore of 0.
f Clinical remission is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the
endoscopy, where the stool frequency subscore has not increased from induction baseline.
g IBDQ remission is defined as a total IBDQ score ≥ 170.

Almost 40% of participants were receiving oral corticosteroids upon entry into the Maintenance Study. Per protocol, participants in clinical response following guselkumab induction were instructed to taper the daily dose of corticosteroids beginning at Week M 0.

- **Numbers analysed**

A total of 846 participants who completed IS-1 or IS-2 and were in clinical response to induction study intervention were enrolled in the Maintenance Study. All enrolled participants were treated

Of the 846 participants treated in the Maintenance Study, 805 (95.2%) participants had a modified Mayo score of 5 to 9 at induction baseline. The primary analysis population for this study consists of 568 participants in the Randomized Full Analysis Set, (ie, participants with a modified Mayo score of 5 to 9 at induction baseline who were randomized and treated in the Maintenance Study.

- **Outcomes and estimation**

*Primary and key secondary endpoints*

**Table 29: Number of Participants Who Achieved the Primary and Major Secondary Endpoints at Week M 44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

| | Placebo SC | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| Randomized Full Analysis Set | 190 | 188 | 190 |
| **Primary Endpoint** | | | |
| Clinical remission[a] | 36 (18.9%) | 85 (45.2%)‡ | 95 (50.0%)‡ |
| **Major Secondary Endpoints** | | | |
| Symptomatic remission[b] | 71 (37.4%) | 132 (70.2%)‡ | 131 (68.9%)‡ |
| Endoscopic healing[c] | 36 (18.9%) | 93 (49.5%)‡ | 98 (51.6%)‡ |
| Corticosteroid-free clinical remission[d] | 35 (18.4%) | 85 (45.2%)‡ | 93 (48.9%)‡ |
| Maintenance of clinical response[e] | 82 (43.2%) | 146 (77.7%)‡ | 142 (74.7%)‡ |
| Histologic-endoscopic mucosal healing[f] | 32 (16.8%) | 82 (43.6%)‡ | 91 (47.9%)‡ |
| IBDQ remission[g] | 71 (37.4%) | 121 (64.4%)‡ | 122 (64.2%)‡ |
| Fatigue response[h] | 56 (29.5%) | 95 (50.5%)‡ | 82 (43.2%)† |
| Maintenance of clinical remission[i] | 20/59 (33.9%) | 40/66 (60.6%)† | 50/69 (72.5%)‡ |
| Endoscopic normalization[j] | 29 (15.3%) | 65 (34.6%)‡ | 64 (33.7%)‡ |

- ‡p<0.001; †p<0.01. p-values were based on the Cochran-Mantel-Haenszel chi-square test.
- Note: Includes only participants with a modified Mayo score 5 to 9 at induction baseline.

a Clinical remission=a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
b Symptomatic remission=a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.
c Endoscopic healing (improvement)=an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
d Corticosteroid-free clinical remission=clinical remission without any use of corticosteroids for ≥8 weeks prior to assessment.
e Maintenance of clinical response=clinical response at Week M-44 among participants in clinical response at maintenance baseline; clinical response=a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.
f Histologic-endoscopic mucosal healing (improvement)=achieving a combination of histologic healing and endoscopic healing.
g IBDQ remission=total Inflammatory Bowel Disease Questionnaire score ≥170.
h Fatigue response=a ≥7-point improvement from induction baseline in PROMIS-Fatigue Short Form 7a.
i Maintenance of clinical remission=clinical remission among participants in clinical remission at maintenance baseline.
j Endoscopic normalization (remission)=an endoscopy subscore of 0.

*Endoscopic and histologic endpoints*

**Table 30: Number of Participants Who Achieved Other Endoscopic and Histologic Efficacy Endpoints (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

| | Placebo SC | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| Randomized Full Analysis Set | 190 | 188 | 190 |
| Histologic healing (ie, Geboes score ≤3.1) at Week M-44 | 58 (30.5%) | 122 (64.9%)‡ | 122 (64.2%)‡ |
| Histologic healing at Week M-44 among participants without histologic healing at induction baseline | 46/170 (27.1%) | 105/160 (65.6%)‡ | 104/159 (65.4%)‡ |
| Histologic remission (ie, Geboes score ≤2B.0) at Week M-44 | 51 (26.8%) | 111 (59.0%)‡ | 115 (60.5%)‡ |
| Histologic-endoscopic mucosal healing (alternative definition, ie, histologic remission and endoscopic healing) at Week M-44 | 30 (15.8%) | 78 (41.5%)‡ | 89 (46.8%)‡ |
| Deep histologic-endoscopic mucosal healing (improvement; ie, histologic remission and endoscopic normalization) at Week M-44 | 27 (14.2%) | 59 (31.4%)‡ | 62 (32.6%)‡ |
| Composite of symptomatic remission, histologic-endoscopic mucosal healing, and fecal calprotectin ≤250 mg/kg at Week M-44 | 21 (11.1%) | 58 (30.9%)‡ | 67 (35.3%)‡ |
| Composite of symptomatic remission, deep histologic-endoscopic mucosal healing, and fecal calprotectin ≤250 mg/kg at Week M-44 | 18 (9.5%) | 42 (22.3%)‡ | 53 (27.9%)‡ |

‡p<0.001. **All p-values are nominal** and were based on the Cochran-Mantel-Haenszel chi-square test.

- Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

*Stool frequency and resolution of rectal bleeding*

Higher proportions of participants in the guselkumab 200 mg and 100 mg groups sustained stool frequency subscore of 0 or 1 and resolution of rectal bleeding (rectal bleeding subscore of 0) through Week M-44 compared with the placebo group. Separation between the guselkumab treatment groups and the placebo group was observed by Week M-12 for participants with a stool frequency subscore of 0 or 1 and by Week M-16 for participants with a rectal bleeding subscore of 0 and continued through Week M-44.

*Corticosteroid Elimination*

Almost 40% of participants were receiving oral corticosteroids upon entry into the Maintenance Study. Per protocol, participants in clinical response following guselkumab induction were instructed to taper their daily dose of corticosteroids beginning at Week M-0.

Among participants who were receiving concomitant oral corticosteroids at maintenance baseline:

- From Week M-8, higher proportions of participants in both guselkumab treatment groups had eliminated oral corticosteroid use compared with the placebo group. Higher proportions of participants in the guselkumab 200 mg (65.8%) and 100 mg (71.2%) groups had eliminated oral corticosteroids at Week M-44 compared with the placebo group (36.0%; nominal p<0.001 for both).
- Higher proportions of participants in the guselkumab 200 mg (39.7%) and 100 mg (47.9%) groups were in clinical remission at Week M-44 AND had eliminated oral corticosteroid use for

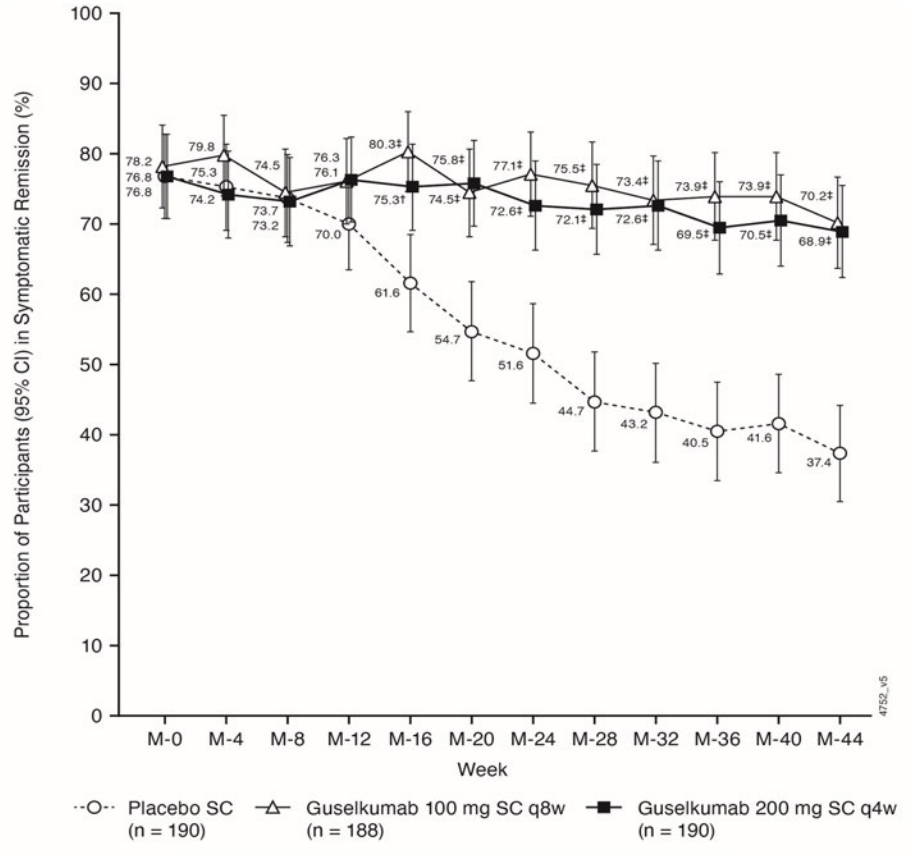
at least 8 weeks prior to Week M-44 compared with the placebo group (13.3%; nominal p<0.001 for both).

- At Week M-44, the mean decreases from maintenance baseline in the average daily prednisone-equivalent dose (excluding budesonide and beclomethasone dipropionate) were greater in the guselkumab treatment groups compared with the placebo group (nominal p<0.001 for both).

**Clinical Outcomes Through Week M 44**

*Symptomatic Remission Over Time*

**Figure 31: Proportion of Participants in Symptomatic Remission Through Week M-44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

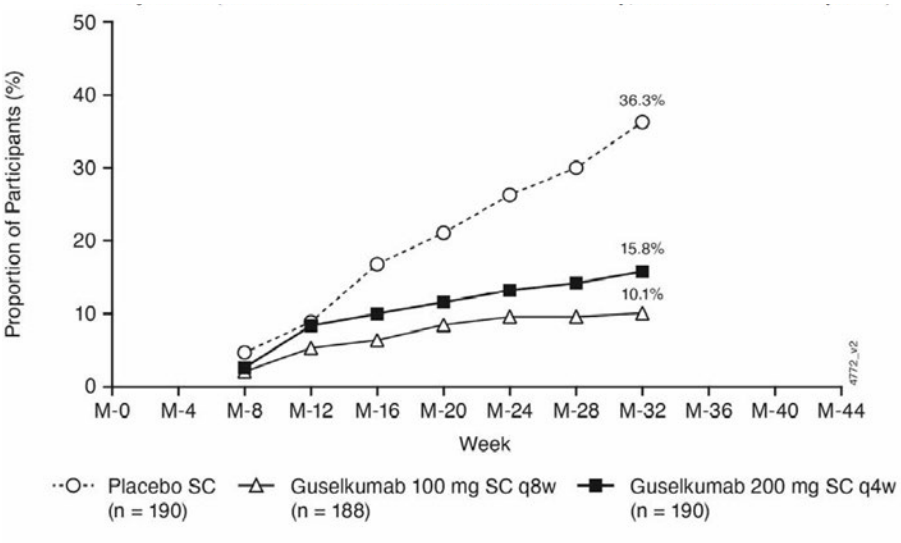



†p<0.01 ‡p<0.001. All p-values except Week M-44 are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.
Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

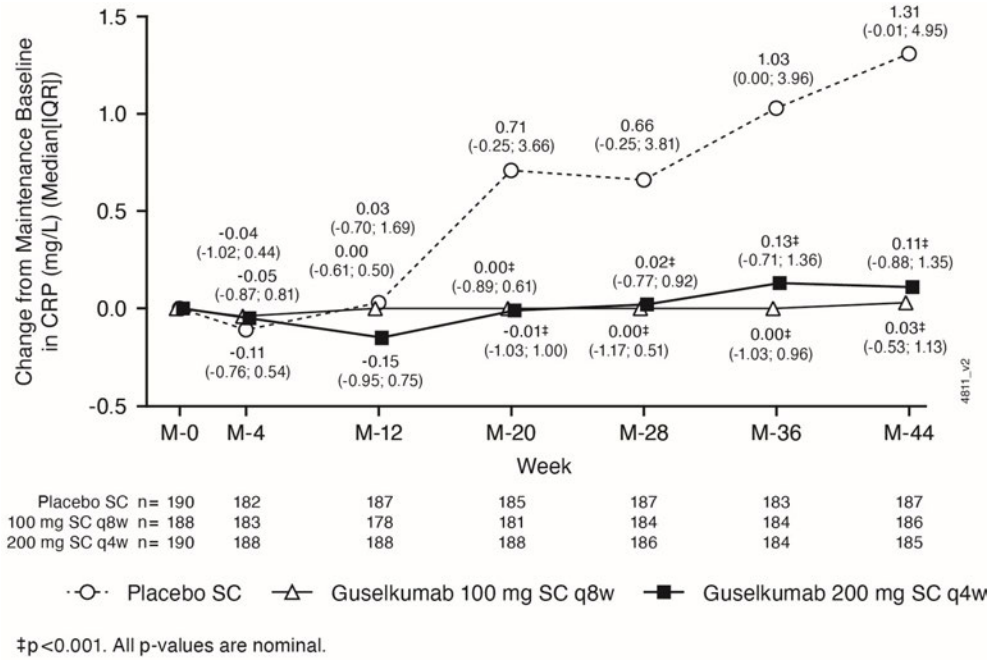
*Loss of therapeutic response*

**Figure 32: Cumulative proportion of participants who met the loss of response criteria for dose adjustment (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**



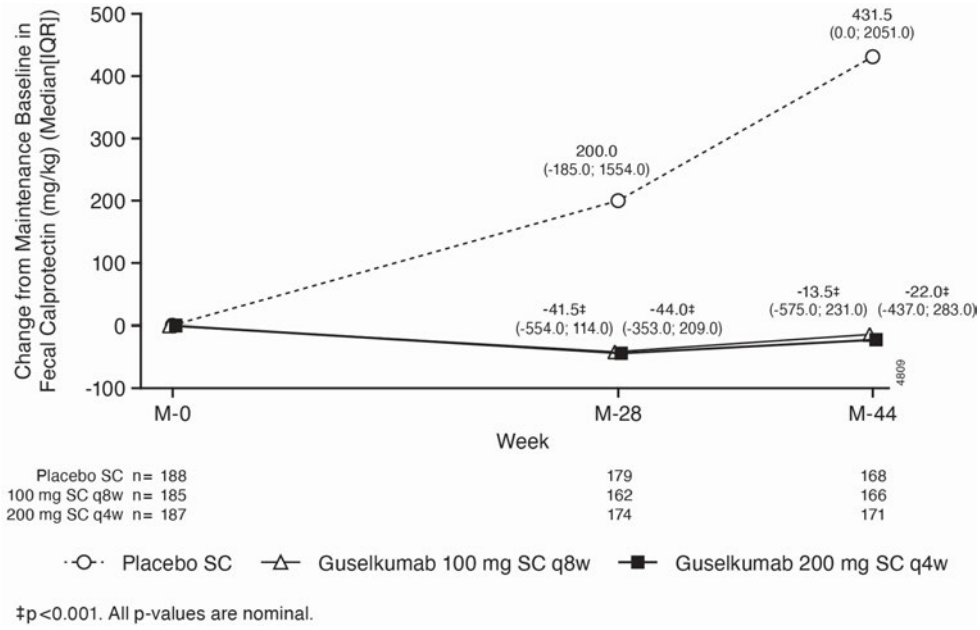

*Inflammatory Biomarkers Through Week M-44*

**Figure 33: Median Change From Maintenance Baseline in CRP Concentration (mg/L) Through Week M-44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**



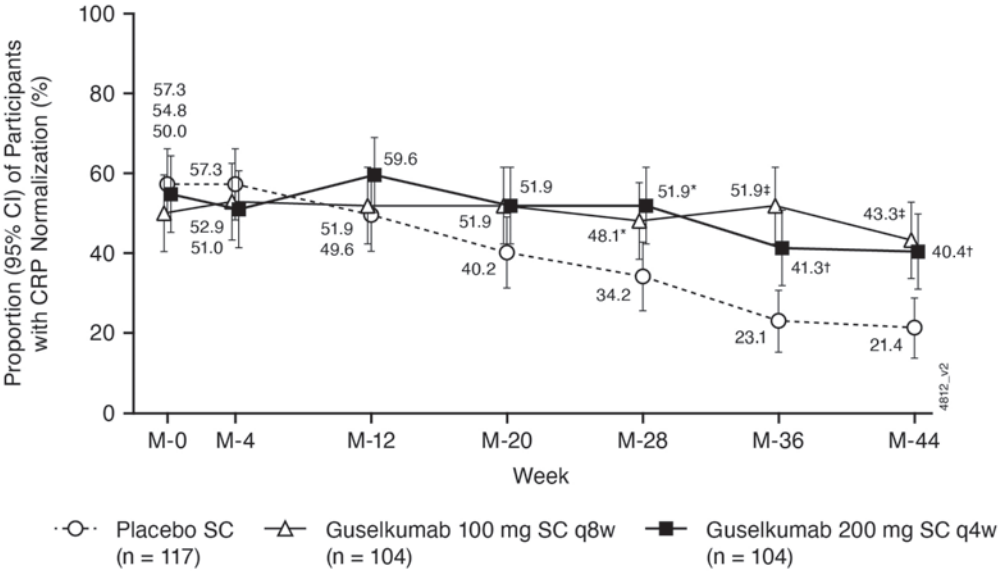

‡p<0.001. All p-values are nominal.

**Figure 34: Median Change From Maintenance Baseline in Fecal Calprotectin Concentration (mg/kg) Through Week M-44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**




‡p<0.001. All p-values are nominal.

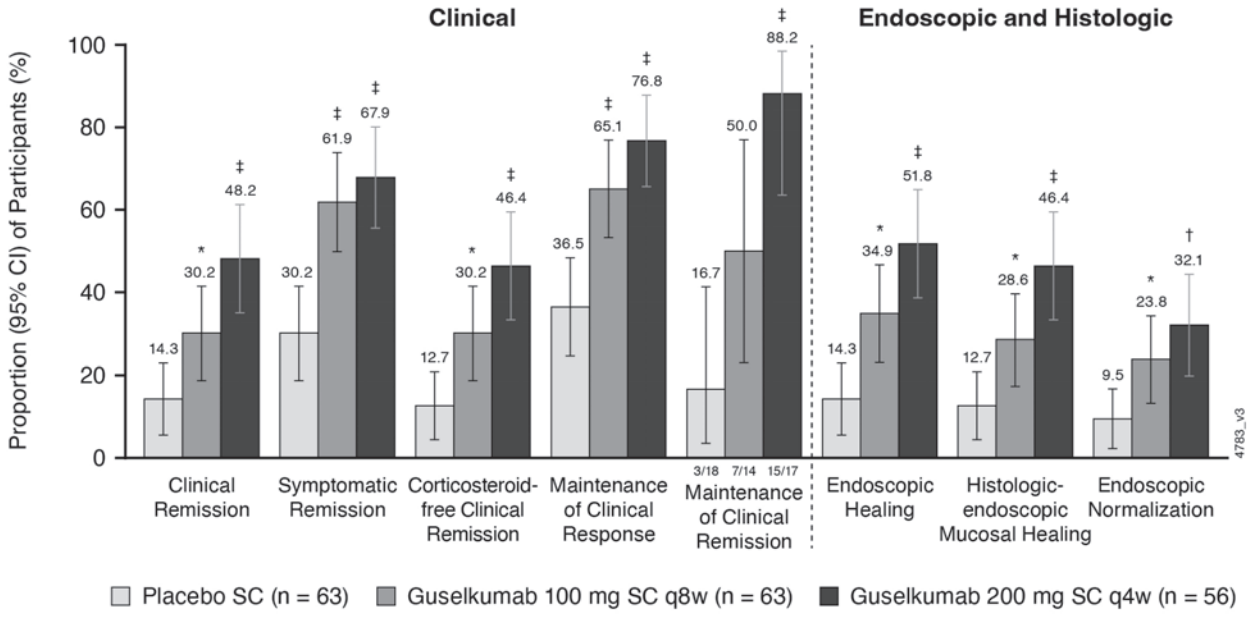
**Figure 35: The Proportion of Participants With Normalized CRP Concentrations Through Week M-44 Among Participants with a CRP >3 mg/L at Induction Baseline (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**




*p<0.05 †p<0.01 ‡p<0.001. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 and an elevated CRP concentration (>3 mg/L) at induction baseline.

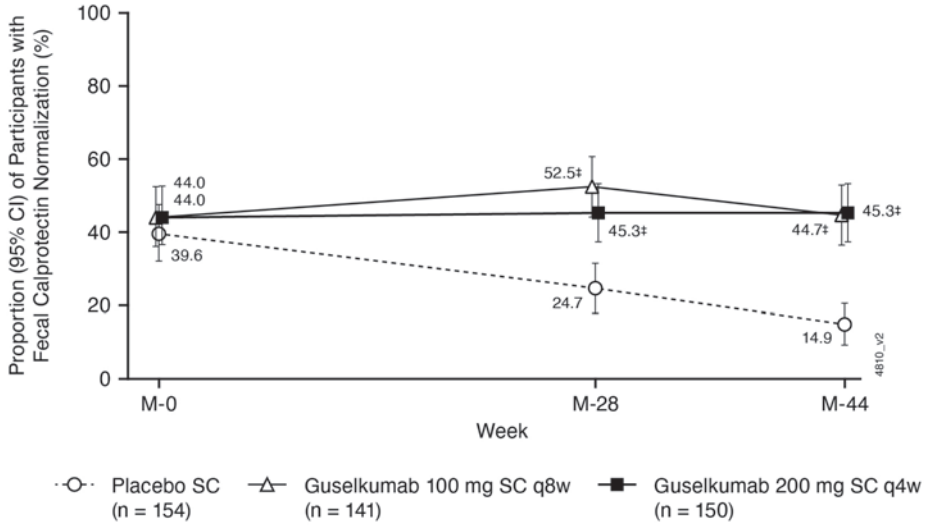
**Figure 36: Key Efficacy Endpoints Among Participants With a CRP >3 mg/L at Maintenance Baseline (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**




*p<0.05 †p<0.01 ‡p<0.001. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline whose CRP concentration was >3 mg/L at maintenance baseline.

**Figure 37: The Proportion of Participants With Normalized Fecal Calprotectin Concentrations Through Week M-44 Among Participants with a Fecal Calprotectin >250 mg/kg at Induction Baseline (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**




‡p<0.001. All p-values are nominal.

Note: Includes only participants with a modified Mayo score of 5-9 and an elevated fecal calprotectin (>250 mg/kg) at induction baseline.

*Patient-reported Outcomes Through Week M-44*

**Table 31: Summary of Patient-reported Outcomes at Week M 44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

| | Placebo SC | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| Randomized Full Analysis Set | 190 | 188 | 190 |
| **PROMIS-Fatigue SF-7a T-score** | | | |
| Change from maintenance baseline at Week M-44 (Mean [SD])[a] | 3.57 (9.501) | -0.51 (9.513) | 0.53 (9.557) |
| Treatment difference in LS Means (95% CI) | | -3.45 (-5.22, -1.68)‡ | -2.37 (-4.15, -0.60)† |
| **Fatigue response at Week M-44** (major secondary endpoint) | | | |
| Participants n (%) | 56 (29.5%) | 95 (50.5%) | 82 (43.2%) |
| Adjusted treatment difference (95% CI) | | 20.1% (10.7%, 29.5%)‡ | 12.6% (3.3%, 21.9%)† |
| **IBDQ total score** | | | |
| Change from maintenance baseline at Week M-44 (Mean [SD])[a] | -27.7 (40.96) | -0.4 (32.57) | -2.9 (33.10) |
| Treatment difference in LS Means (95% CI) | | 25.6 (18.6, 32.6)‡ | 23.3 (16.3, 30.3)‡ |
| **IBDQ remission at Week M-44** (major secondary endpoint) | | | |
| Participants n (%) | 71 (37.4%) | 121 (64.4%) | 122 (64.2%) |
| Adjusted treatment difference in LS Means (95% CI) | | 26.3% (16.8%, 35.7%)‡ | 25.9% (16.5%, 35.4%)‡ |
| **Bowel urgency severity** | | | |
| Participants with a ≥2-point improvement in bowel urgency severity from induction baseline at maintenance baseline | 120 | 121 | 118 |
| Participants who maintained a ≥2-point improvement in bowel urgency severity through Week M-44[b] | 43 (35.8%) | 80 (66.1%) | 74 (62.7%) |
| Adjusted treatment difference (95% CI) | | 29.0% (17.2%, 40.9%)‡ | 26.3% (14.4%, 38.3%)‡ |
| **Impact of bowel urgency** | | | |
| Participants with a ≥2-point improvement in impact of bowel urgency from induction baseline at maintenance baseline | 103 | 89 | 91 |
| Participants who maintained a ≥2-point improvement in impact of bowel urgency through Week M-44[b] | 38 (36.9%) | 67 (75.3%) | 65 (71.4%) |
| Adjusted treatment difference (95% CI) | | 38.0% (25.2%, 50.9%)‡ | 34.8% (22.1%, 47.4%)‡ |
| **Abdominal pain** | | | |
| Participants with a ≥2-point improvement in abdominal pain from induction baseline at maintenance baseline | 105 | 98 | 104 |
| Participants who maintained a ≥2-point improvement in abdominal pain through Week M-44[b] | 37 (35.2%) | 68 (69.4%) | 63 (60.6%) |
| Adjusted treatment difference (95% CI) | | 33.6% (20.7%, 46.5%)‡ | 24.6% (11.7%, 37.5%)‡ |

| | Placebo SC | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| **PROMIS-29 PCS T-score** | | | |
| Change from maintenance baseline at Week M-44 (Mean [SD])[a] | -2.58 (7.916) | 0.06 (7.532) | 0.77 (7.511) |
| Treatment difference in LS Means (95% CI) | | 2.54 (1.12, 3.96)‡ | 3.04 (1.62, 4.46)‡ |
| Participants with a ≥7-point improvement in PROMIS-29 PCS from induction baseline at maintenance baseline | 74 | 85 | 68 |
| Participants who maintained a ≥7-point improvement in PROMIS-29 PCS through Week M-44[c] | 32 (43.2%) | 55 (64.7%) | 43 (63.2%) |
| Adjusted treatment difference (95% CI) | | 20.5% (5.7%, 35.2%)† | 18.6% (3.0%, 34.1%)* |
| **PROMIS-29 MCS T-score** | | | |
| Change from maintenance baseline at Week M-44 (Mean [SD])[a] | -4.34 (7.822) | 0.61 (8.134) | -0.23 (8.033) |
| Treatment difference in LS Means (95% CI) | | 4.64 (3.11, 6.16)‡ | 3.81 (2.28, 5.34)‡ |
| Participants with a ≥7-point improvement in PROMIS-29 MCS from induction baseline at maintenance baseline | 107 | 96 | 94 |
| Participants who maintained a ≥7-point improvement in PROMIS-29 MCS through Week M-44[c] | 37 (34.6%) | 64 (66.7%) | 58 (61.7%) |
| Adjusted treatment difference (95% CI) | | 31.4% (18.5%, 44.4%)‡ | 25.7% (12.8%, 38.7%)‡ |
| **EQ-VAS** | | | |
| Change from maintenance baseline at Week M-44 (Mean [SD])[a] | -10.7 (21.69) | 0.3 (20.01) | -1.2 (20.64) |
| Treatment difference in LS Means (95% CI) | | 10.9 (7.0, 14.7)‡ | 9.2 (5.3, 13.1)‡ |

‡p<0.001; †p≤0.01; *p<0.05. **All p-values were nominal except for fatigue response and IBDQ remission.**
Note: Includes only participants with modified Mayo score 5-9 at induction baseline.
a For change from baseline analyses: N=184 (placebo SC); N=184 (guselkumab 100 mg SC q8w); N=181 (guselkumab 200 mg SC q4w).
b Maintenance of a ≥2-point improvement from induction baseline is defined as a ≥2-point improvement from induction baseline at both Week M-28 and Week M-44 among participants with a ≥2-point improvement from induction baseline at maintenance baseline.
c Maintenance of a ≥7-point improvement from induction baseline is defined as a ≥7-point improvement from induction baseline at both Week M-28 and Week M-44 among participants with a ≥7-point improvement from induction baseline at maintenance baseline.

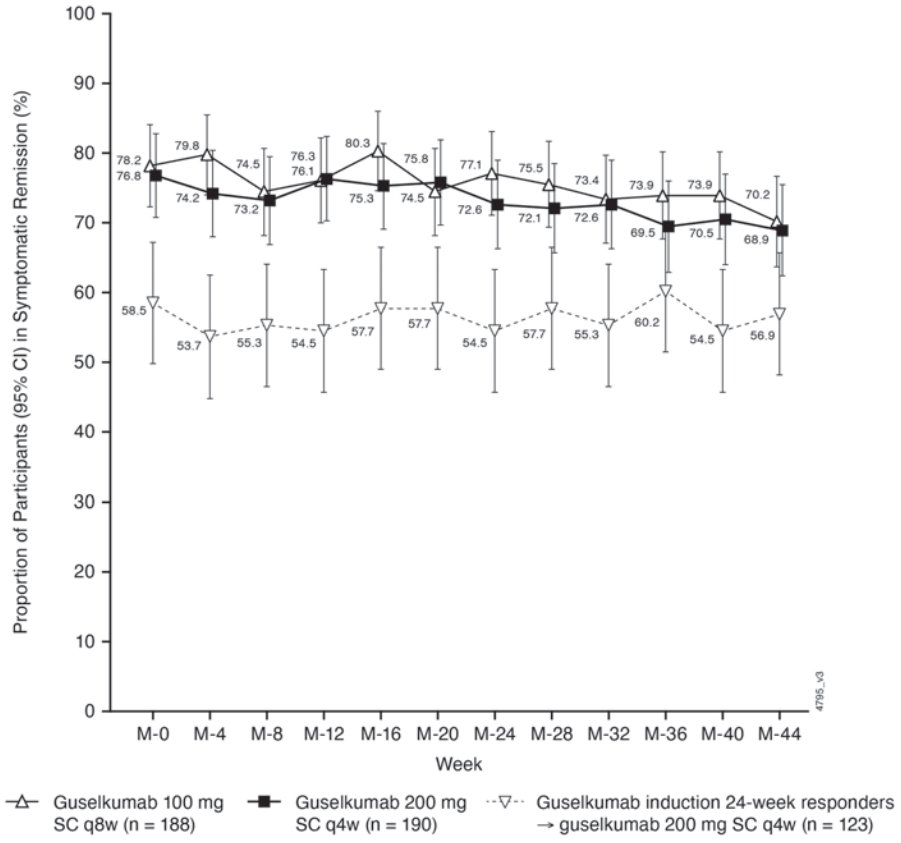
### Guselkumab Induction 24-week Responders

**Table 32: Summary of Key Efficacy Endpoints at Week M 44 (CNTO1959UCO3001 Phase 3 Maintenance Study; Guselkumab 24 week Responders)**

| | Guselkumab Induction 24-week Responders[a] → Guselkumab 200 mg SC q4w |
|---|---|
| N | 123 |
| Clinical remission at Week M-44 | 37 (30.1%) |
| Symptomatic remission at Week M-44 | 70 (56.9%) |
| Endoscopic healing at Week M-44 | 44 (35.8%) |
| Corticosteroid-free clinical remission at Week M-44 | 37 (30.1%) |
| Maintenance of clinical response at Week M-44 | 83 (67.5%) |
| Histologic-endoscopic mucosal healing at Week M-44 | 34 (27.6%) |
| IBDQ remission at Week M-44 | 67 (54.5%) |
| Fatigue response at Week M-44 | 49 (39.8%) |
| Maintenance of clinical remission at Week M-44 | 10/20 (50.0%) |
| Endoscopic normalization at Week M-44 | 21 (17.1%) |

- Note: Includes only participants with a modified Mayo score 5-9 at induction baseline.
- a Participants initially randomized to guselkumab IV who were not in clinical response at Week I-12 who then received 3 doses of guselkumab 200 mg SC q4w and achieved clinical response at Week I-24.

**Figure 38: Symptomatic Remission Among Guselkumab Treatment Groups Through Week M 44 (CNTO1959UCO3001 Maintenance Study; Randomized Full Analysis and Nonrandomized Full Analysis Sets)**




Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

Guselkumab induction 24-Week responders are participants initially randomized to IV guselkumab who were not in clinical response at Week I-12 who then received 3 doses of guselkumab 200 mg SC and achieved clinical response at Week I-24.

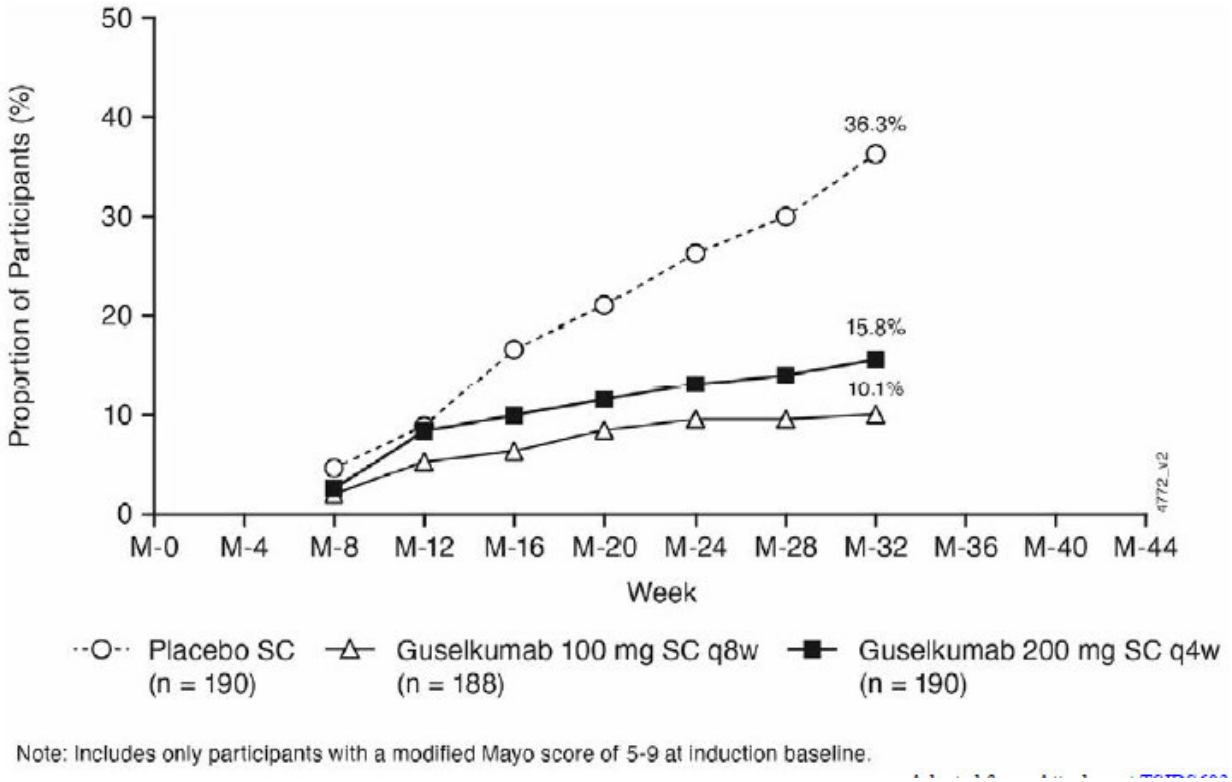
**Corticosteroids elimination**

Among participants who were receiving concomitant oral corticosteroids at maintenance baseline:

- As early as Week M 8, higher proportions of participants in both guselkumab treatment groups had eliminated oral corticosteroid use compared with the placebo group. Higher proportions of participants in the guselkumab 200 mg (65.8%) and 100 mg (71.2%) groups had eliminated oral corticosteroids at Week M 44 compared with the placebo group (36.0%; nominal p<0.001 for both).
- Higher proportions of participants in the guselkumab 200 mg (39.7%) and 100 mg (47.9%) groups were in clinical remission at Week M 44 and had eliminated oral corticosteroid use for at least 8 weeks prior to Week M 44 compared with the placebo group (13.3%; nominal p<0.001 for both).
- At Week M 44, the mean decreases from maintenance baseline in the average daily prednisone-equivalent dose (excluding budesonide and beclomethasone dipropionate) were greater in the guselkumab treatment groups compared with the placebo group (nominal p<0.001 for both).

**Loss of response**

**Table 33: Cumulative Proportion of Participants who Met the Loss of Response Criteria for Dose Adjustment (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**




Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

Upon the CHMP's request, the MAH presented and discussed the time course of the primary and key secondary efficacy response rate endpoints for ADT naive and ADT failed subgroups of the Guselkumab Week 24 responder patients.

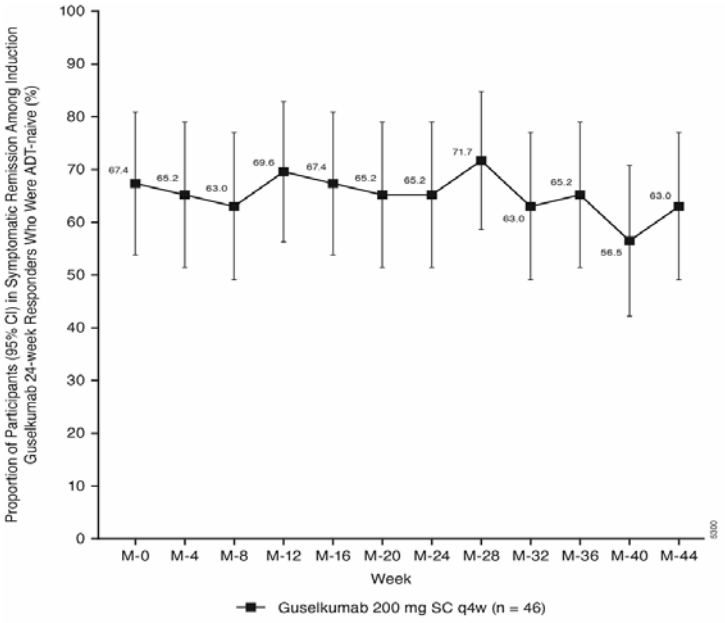
**Table 34: Summary of Key Efficacy Endpoints at Week M-44 Among Induction Guselkumab 24-Week Responders; Nonrandomized Full Analysis Set (Study CNTO1959UCO3001; Maintenance)**

| | ADT-naive | ADT-failed |
|---|---|---|
| | Induction Guselkumab 24-week Responders[a] | Induction Guselkumab 24-week Responders[a] |
| | Nonrandomized Guselkumab 200 mg SC q4w | Nonrandomized Guselkumab 200 mg SC q4w |
| Analysis set: Nonrandomized Full | 123 | 123 |
| | | |
| Subjects in the respective prior ADT use subgroup | 46 (37.4%) | 73 (59.3%) |
| | | |
| Subjects in clinical remission at Week M-44[b1,c,d,e] | 18 (39.1%) | 19 (26.0%) |
| 95% CI for treatment proportion[f] | (25.0%, 53.2%) | (16.0%, 36.1%) |
| | | |
| Subjects in symptomatic remission at Week M-44[b2,c,d,e] | 29 (63.0%) | 40 (54.8%) |
| 95% CI for treatment proportion[f] | (49.1%, 77.0%) | (43.4%, 66.2%) |
| | | |
| Subjects with endoscopic healing at Week M-44[b3,c,d,e] | 20 (43.5%) | 23 (31.5%) |
| 95% CI for treatment proportion[f] | (29.2%, 57.8%) | (20.9%, 42.2%) |
| | | |
| Subjects in corticosteroid-free clinical remission at Week M-44[b4,c,d,e] | 18 (39.1%) | 19 (26.0%) |
| 95% CI for treatment proportion[f] | (25.0%, 53.2%) | (16.0%, 36.1%) |
| | | |
| Subjects in clinical response at Week M-44[b5,c,d,e] | 33 (71.7%) | 49 (67.1%) |
| 95% CI for treatment proportion[f] | (58.7%, 84.8%) | (56.3%, 77.9%) |
| | | |
| Subjects with histologic-endoscopic mucosal healing at Week M-44[b6,c,d,e] | 19 (41.3%) | 14 (19.2%) |
| 95% CI for treatment proportion[f] | (27.1%, 55.5%) | (10.1%, 28.2%) |
| | | |
| Subjects in IBDQ remission at Week M-44[b7,c,d,e] | 27 (58.7%) | 39 (53.4%) |
| 95% CI for treatment proportion[f] | (44.5%, 72.9%) | (42.0%, 64.9%) |
| | | |
| Subjects in fatigue response at Week M-44[b8,c,d,e] | 21 (45.7%) | 26 (35.6%) |
| 95% CI for treatment proportion[f] | (31.3%, 60.0%) | (24.6%, 46.6%) |
| | | |
| Subjects in clinical remission at maintenance baseline[b1,c] | 10 (21.7%) | 9 (12.3%) |
| Subjects in clinical remission at Week M-44[b1,d,e,g] | 6 (60.0%) | 4 (44.4%) |
| 95% CI for treatment proportion[h] | (26.2%, 87.8%) | (13.7%, 78.8%) |

| | | |
|---|---|---|
| Subjects with endoscopic normalization at Week M-44[b9,c,d,e] | 12 (26.1%) | 9 (12.3%) |
| 95% CI for treatment proportion[f] | (13.4%, 38.8%) | (4.8%, 19.9%) |

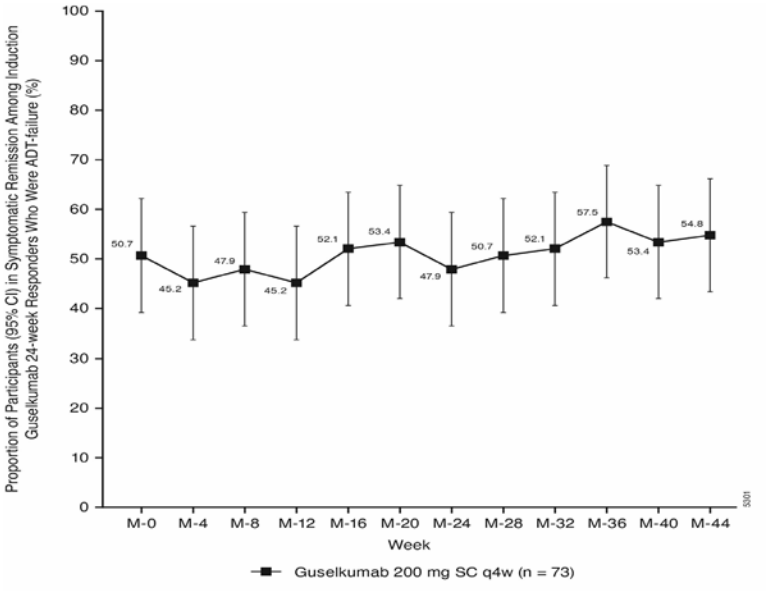
Key: ADT=advanced therapy.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
[a] Subjects who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab from Week I-12.
[b1] Clinical remission is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
[b2] Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline.
[b3] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
[b4] Corticosteroid-free clinical remission is defined as not requiring any treatment with corticosteroids for at least 8 weeks prior to Week M-44 and also meeting the criteria for clinical remission at Week M-44.
[b5] Clinical response is defined as a decrease from induction baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.
[b6] Histologic-endoscopic mucosal healing is defined as achieving a combination of histologic healing and endoscopic healing. Histologic healing is defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system.
[b7] IBDQ (Inflammatory Bowel Disease Questionnaire) remission is defined as a total IBDQ score ≥ 170.
[b8] Fatigue response is defined as ≥ 7-point improvement from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) Fatigue Short Form 7a.
[b9] Endoscopic normalization is defined as an endoscopy subscore of 0.
[c] Denominator is induction guselkumab 24-week responders who were ADT-naive.
[d] Intercurrent Event (ICE) Strategies: Subjects who had an ostomy or colectomy (ICE 1), a prohibited change in UC medications (ICE 3), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 4) prior to Week M-44 were considered not to have achieved any of the key efficacy endpoints shown at Week M-44. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 5) prior to Week M-44, their observed values (if available) were used. Subjects who experienced ICE 6 (discontinued study agent due to reasons other than those in ICEs 4 and 5) prior to Week M-44 were considered not to have achieved any of the key efficacy endpoints shown at Week M-44.
[e] Nonresponder Imputation for Missing Data: Subjects who were missing one or more of the components pertaining to an endpoint at Week M-44 were considered not to have achieved the endpoint. Subjects who had an unevaluable biopsy (i.e., a biopsy that was collected, but could not be assessed due to sample preparation or technical errors) were considered not to have achieved the histology endpoints.
[f] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the normal approximation confidence limits.
[g] Denominator is based on the subjects in clinical remission at maintenance baseline who were induction guselkumab 24-week responders and were ADT-naive.
[h] The confidence intervals for the proportion of subjects meeting the endpoint in each treatment group were based on the exact confidence limits.

**Figure 39: Proportion of Participants in Symptomatic Remission Through Week M-44 Among Induction Guselkumab 24-week Responders; Nonrandomized Full Analysis Set (Study CNTO1959UCO3001; Maintenance)**




Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.
Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

**Figure 40: Proportion of Participants in Symptomatic Remission Through Week M-44 Among Induction Guselkumab 24-week Responders Who Were ADT-failure; Nonrandomized Full Analysis Set (Study CNTO1959UCO3001; Maintenance)**




Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.
Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

**Dose Adjustment**

Participants randomized to guselkumab who met the criteria for loss of clinical response during the maintenance study, which was based on the modified Mayo score and required an endoscopic

assessment, were allowed a single blinded dose adjustment to the guselkumab 200 mg SC q4w dose regimen.

*Guselkumab 100 mg SC q8w → Guselkumab 200 mg SC q4w*

After meeting the loss of clinical response criteria during the Maintenance Study, 19 participants in the guselkumab 100 mg SC q8w group had a dose adjustment to guselkumab 200 mg SC q4w. These participants had up to 50% lower serum guselkumab concentrations compared with participants in the 100 mg SC q8w group who did not meet loss of response criteria.

Following the dose adjustment, the number of participants in symptomatic response and symptomatic remission increased 4 weeks after dose adjustment. Eleven participants (57.9%) were in symptomatic response, and 5 participants (26.3%) were in symptomatic remission 12 weeks after the dose adjustment. The efficacy observed following the dose adjustment from guselkumab 100 mg SC q8w to 200 mg SC q4w was accompanied by an increase in median trough guselkumab concentrations (from 0.73 µg/mL to 6.51 µg/mL). However, the very low number of patients precludes drawing any further conclusion on this.

*Guselkumab 200 mg SC q4w → Guselkumab 200 mg SC q4w*

Participants randomized to guselkumab 200 mg SC q4w who met the criteria for loss of response received a sham dose adjustment and continued to receive guselkumab 200 mg SC q4w. Thirty participants randomized to guselkumab 200 mg SC q4w who met the criteria for loss of response received a sham dose adjustment (guselkumab 200 mg SC q4w → guselkumab 200 mg SC q4w). Twenty two participants (73.3%) were in symptomatic response, and 12 participants (40.0%) were in symptomatic remission 12 weeks after the sham dose adjustment.

*Participants Who Resumed Guselkumab After a Treatment Interruption: Placebo SC → Guselkumab 200 mg SC q4w*

Participants randomized to the placebo SC group in the Maintenance Study, who met the loss of response criteria, were eligible for a dose adjustment to guselkumab 200 mg SC q4w between Week M 8 and Week M 32.

Of the 69 participants randomized to placebo who met the loss of response criteria, the number of participants in symptomatic response and symptomatic remission increased 4 weeks after a dose adjustment to guselkumab 200 mg SC q4w and continued to improve with 62 participants (89.9%) in symptomatic response and 44 participants (63.8%) in symptomatic remission 12 weeks after resuming guselkumab.

- **Ancillary analyses**

**Primary and major secondary endpoints**

Prespecified subgroup analyses were conducted based on ADT-failure status, baseline clinical status, guselkumab induction dose received, inflammatory biomarker thresholds, and baseline body weight for key efficacy endpoints including primary, major secondary, and other selected histologic and endoscopic efficacy endpoints. The treatment effects of guselkumab within these subgroups were generally consistent with those observed in the primary analysis population. The guselkumab induction dose received (400 mg IV or 200 mg IV) did not have an apparent effect on efficacy in the Maintenance Study.

*ADT-failure Status*

In the primary analysis population, 42.3% had a history of ADT failure, 54.4% were ADT naïve, and 3.3% were ADT experienced without documented failure.

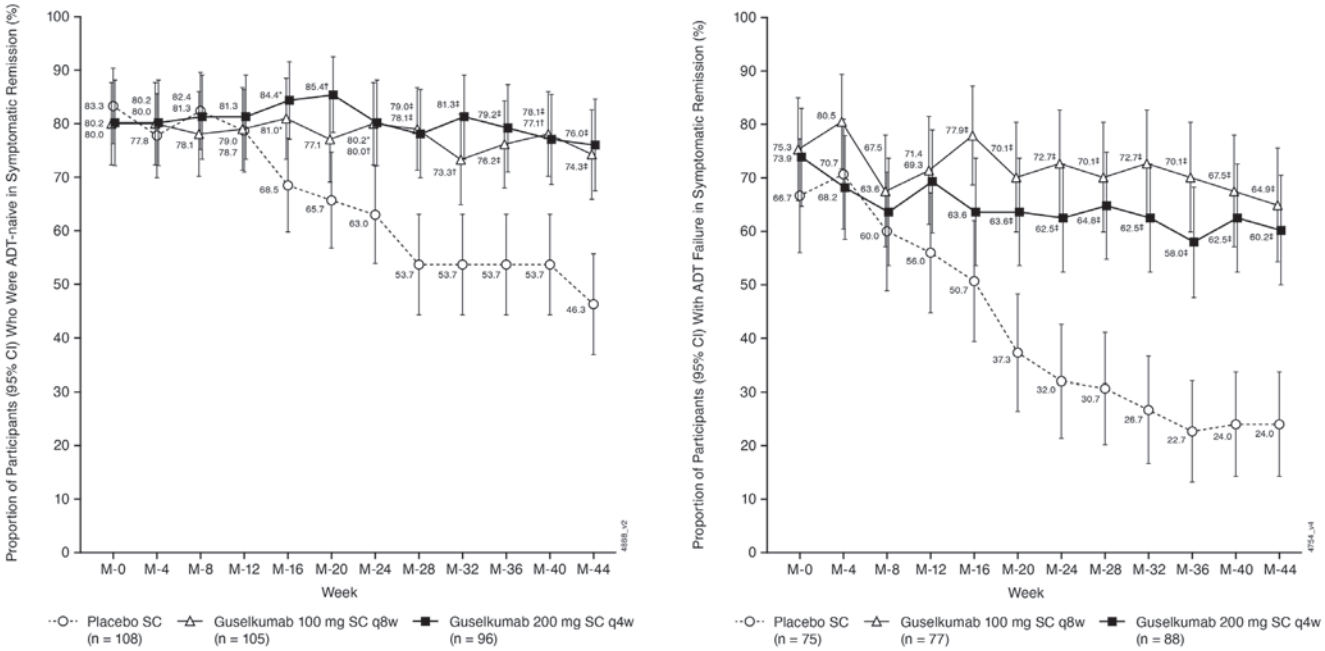
**Table 35: Key Endpoints at Week M 44 by Induction Baseline ADT-failure Status (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

| | ADT-naïve | | | ADT-nonfailure | | | ADT-failure | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Guselkumab | | | Guselkumab | | | Guselkumab | |
| | Placebo SC | 100 mg SC q8w | 200 mg SC q4w | Placebo SC | 100 mg SC q8w | 200 mg SC q4w | Placebo SC | 100 mg SC q8w | 200 mg SC q4w |
| N | 108 | 105 | 96 | 115 | 111 | 102 | 75 | 77 | 88 |
| Clinical remission | 28 (25.9%) | 53 (50.5%)‡ | 56 (58.3%)‡ | 30 (26.1%) | 54 (48.6%)‡ | 60 (58.8%)‡ | 6 (8.0%) | 31 (40.3%)‡ | 35 (39.8%)‡ |
| Symptomatic remission | 50 (46.3%) | 78 (74.3%)‡ | 73 (76.0%)‡ | 53 (46.1%) | 82 (73.9%)‡ | 78 (76.5%)‡ | 18 (24.0%) | 50 (64.9%)‡ | 53 (60.2%)‡ |
| Endoscopic healing | 28 (25.9%) | 56 (53.3%)‡ | 57 (59.4%)‡ | 30 (26.1%) | 58 (52.3%)‡ | 61 (59.8%)‡ | 6 (8.0%) | 35 (45.5%)‡ | 37 (42.0%)‡ |
| Corticosteroid-free clinical remission | 28 (25.9%) | 53 (50.5%)‡ | 54 (56.3%)‡ | 30 (26.1%) | 54 (48.6%)‡ | 58 (56.9%)‡ | 5 (6.7%) | 31 (40.3%)‡ | 35 (39.8%)‡ |
| Maintenance of clinical response | 58 (53.7%) | 87 (82.9%)‡ | 78 (81.3%)‡ | 61 (53.0%) | 92 (82.9%)‡ | 83 (81.4%)‡ | 21 (28.0%) | 54 (70.1%)‡ | 59 (67.0%)‡ |
| Histologic-endoscopic mucosal healing | 25 (23.1%) | 52 (49.5%)‡ | 54 (56.3%)‡ | 26 (22.6%) | 53 (47.7%)‡ | 57 (55.9%)‡ | 6 (8.0%) | 29 (37.7%)‡ | 34 (38.6%)‡ |
| IBDQ remission | 53 (49.1%) | 71 (67.6%)† | 71 (74.0%)‡ | 57 (49.6%) | 76 (68.5%)† | 75 (73.5%)‡ | 14 (18.7%) | 45 (58.4%)‡ | 47 (53.4%)‡ |
| Fatigue response | 39 (36.1%) | 54 (51.4%)* | 51 (53.1%)* | 42 (36.5%) | 59 (53.2%)* | 54 (52.9%)* | 14 (18.7%) | 36 (46.8%)‡ | 28 (31.8%) |
| Maintenance of clinical remission | 14/41 (34.1%) | 28/43 (65.1%)† | 38/48 (79.2%)‡ | 16/44 (36.4%) | 28/46 (60.9%)* | 40/51 (78.4%)‡ | 4/15 (26.7%) | 12/20 (60.0%) | 10/18 (55.6%) |
| Endoscopic normalization | 22 (20.4%) | 40 (38.1%)† | 40 (41.7%)† | 23 (20.0%) | 41 (36.9%)† | 43 (42.2%)† | 6 (8.0%) | 24 (31.2%)‡ | 21 (23.9%)† |

‡ p<0.001; †p<0.01; *p<0.05. **All p-values are nominal.**
Note: Includes only participants with modified Mayo score 5-9 at induction baseline.

**Figure 41:Symptomatic Remission Through Week M-44 by Induction Baseline ADT-failure Status (CNTO1959UCO3001 Phase 3 Maintenance Study; Randomized Full Analysis Set)**

**ADT-naïve** **ADT-failure**




*p<0.05 †p≤0.01 ‡p<0.001. All p-values are nominal.

ADT=advanced therapy

Note: Includes only participants with a modified Mayo score of 5-9 at induction baseline.

Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

**Participants with an induction baseline Modified Mayo Score of 4**

IS-1 and IS-2 enrolled up to 5% of participants with an induction baseline modified Mayo score of 4.

**Table 36: Summary of Key Efficacy Endpoints at Week I 12 Among Randomized and Treated Participants With a Modified Mayo Score of 4 at Induction Baseline (CNTO1959UCO3001 Induction Study 1 and Induction Study 2)**

| | Placebo IV | Guselkumab 200 mg IV |
|---|---|---|
| Participants with a modified Mayo score of 4 at induction baseline | 18 | 26 |
| Clinical remission at Week I-12 | 4 (22.2%) | 14 (53.8%) |
| Symptomatic remission at Week I-12 | 10 (55.6%) | 23 (88.5%)* |
| Endoscopic healing at Week I-12 | 4 (22.2%) | 15 (57.7%)* |
| Clinical response at Week I-12 | 6 (33.3%) | 21 (80.8%)† |
| Symptomatic remission at Week I-4 | 7 (38.9%) | 19 (73.1%)* |
| IBDQ remission at Week I-12 | 10 (55.6%) | 23 (88.5%)* |
| Histologic-endoscopic mucosal healing at Week I-12 | 4 (22.2%) | 11 (42.3%) |
| Fatigue response at Week I-12 | 1 (5.6%) | 11 (42.3%)* |
| Symptomatic remission at Week I-2 | 9 (50.0%) | 17 (65.4%) |
| Endoscopic normalization at Week I-12 | 2 (11.1%) | 9 (34.6%) |

- †p<0.01; *p<0.05. **All p-values are nominal.**
- Endpoints are shown in the order of the Phase 3 testing procedure.

**Table 37: Summary of Key Efficacy Endpoints at Week M-44 Among Randomized and Treated Participants With a Modified Mayo Score of 4 at Induction Baseline (CNTO1959UCO3001 Maintenance Study)**

| | Placebo SC | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| Participants with a modified Mayo score of 4 at induction baseline | 11 | 11 | 9 |
| Clinical remission | 1 (9.1%) | 5 (45.5%) | 3 (33.3%) |
| Symptomatic remission | 4 (36.4%) | 6 (54.5%) | 7 (77.8%) |
| Endoscopic healing | 1 (9.1%) | 5 (45.5%) | 4 (44.4%) |
| Corticosteroid-free clinical remission | 1 (9.1%) | 5 (45.5%) | 3 (33.3%) |
| Maintenance of clinical response | 4 (36.4%) | 5 (45.5%) | 7 (77.8%) |
| Histologic-endoscopic mucosal healing | 1 (9.1%) | 4 (36.4%) | 4 (44.4%) |
| IBDQ remission | 5 (45.5%) | 5 (45.5%) | 8 (88.9%) |
| Fatigue response | 3 (27.3%) | 3 (27.3%) | 1 (11.1%) |
| Maintenance of clinical remission | 0/7 | 3/5 (60.0%) | 2/5 (40.0%) |
| Endoscopic normalization | 1 (9.1%) | 5 (45.5%) | 3 (33.3%) |

- **Summary of main efficacy results**

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 38: Summary of Efficacy for trial CNTO1959UCO3001 (QUASAR: Induction Study 2 [Phase 3 Induction Study])**

| **Title**: **A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis** | | | |
|---|---|---|---|
| Study identifier | CNTO1959UCO3001 | | |
| Design | Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 12 Weeks<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Guselkumab 200 mg IV | | Guselkumab 200 mg administered intravenously at Weeks 0, 4, and 8. |
| | Placebo | | Placebo administered intravenously at Weeks 0, 4, and 8. |
| Endpoints and definitions | Primary endpoint | Clinical remission at Week 12 | A stool frequency subscore of 0 or 1 and not increased from induction baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present. |
| | Major secondary endpoint | Symptomatic remission at Week 12 | A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0. |

| | | | |
|---|---|---|---|
| | Major secondary endpoint | Endoscopic healing at Week 12 | An endoscopy subscore of 0 or 1 with no friability present. |
| | Major secondary endpoint | Clinical response at Week 12 | A decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. |
| | Major secondary endpoint | Symptomatic remission at Week 4 | A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0. |
| | Major secondary endpoint | IBDQ remission at Week 12 | Total IBDQ score ≥170. |
| | Major secondary endpoint | Histologic-endoscopic mucosal healing at Week 12 | A combination of histologic healing (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes2) grading system) and endoscopic healing, as defined above. |
| | Major secondary endpoint | Fatigue response at Week 12 | A ≥7-point improvement from induction baseline in PROMIS-Fatigue short form 7a. |
| | Major secondary endpoint | Symptomatic remission at Week 2 | A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0. |
| | Major secondary endpoint | Endoscopic normalization at Week 12 | An endoscopy subscore of 0. |
| Database lock | 12 January 2023 (date of last observation recorded as part of the database lock for Induction Study 2) | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Full Analysis Set: randomized participants with a baseline modified Mayo score of 5 to 9 who received at least 1 (partial or complete) dose of study intervention. | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number of subjects | 421 | 280 |
| | Number (%) of participants who achieved clinical remission at Week 12 | 95 (22.6%) | 22 (7.9%) |
| | | Comparison groups | Guselkumab 200 mg IV vs placebo |

| | | | |
|---|---|---|---|
| Effect estimates per comparison | Primary endpoint: Clinical remission at Week 12 | Adjusted treatment difference (95% CI) | 14.9% (9.9%, 19.9%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved symptomatic remission at Week 12 | 210 (49.9%) | 58 (20.7%) |
| Effect estimates per comparison | Major secondary endpoint: Symptomatic remission at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 29.4% (22.8%, 36.0%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved Endoscopic healing at Week 12 | 113 (26.8%) | 31 (11.1%) |
| Effect estimates per comparison | Major secondary endpoint: Endoscopic healing at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 16.0% (10.5%, 21.4%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved clinical response at Week 12 | 259 (61.5%) | 78 (27.9%) |
| Effect estimates per comparison | Major secondary endpoint: Clinical response at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 33.8% (26.9%, 40.7%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved symptomatic remission at Week 4 | 95 (22.6%) | 36 (12.9%) |
| Effect estimates per comparison | Major secondary endpoint: Symptomatic remission at Week 4 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 9.9% (4.4%, 15.4%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved IBDQ remission at Week 12 | 216 (51.3%) | 83 (29.6%) |

| | | | |
|---|---|---|---|
| Effect estimates per comparison | Major secondary endpoint: IBDQ remission at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 21.9% (14.9%, 29.0%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved histologic-endoscopic mucosal healing at Week 12 | 99 (23.5%) | 21 (7.5%) |
| Effect estimates per comparison | Major secondary endpoint: Histologic-endoscopic mucosal healing at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 16.2% (11.1%, 21.2%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved fatigue response at Week 12 | 173 (41.1%) | 60 (21.4%) |
| Effect estimates per comparison | Major secondary endpoint: Fatigue response at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 19.8% (13.1%, 26.4%) |
| | | Multiplicity-adjusted P-value | <0.001 |
| **Analysis description** | **Major Secondary Analysis** | | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieve symptomatic remission at Week 2 | 51 (12.1%) | 26 (9.3%) |
| Effect estimates per comparison | Major secondary endpoint: Symptomatic remission at Week 2 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 3.0% (-1.5%, 7.5%) |
| | | Multiplicity-adjusted P-value | 0.210 |
| **Analysis description** | **Major Secondary Analysis** | | |
| Analysis population and time point description | Full Analysis Set | | |
| Descriptive statistics and estimate variability | Treatment group | Guselkumab 200 mg IV | Placebo |
| | Number (%) of participants who achieved endoscopic normalization at Week 12 | 63 (15.0%) | 14 (5.0%) |
| Effect estimates per comparison | Major secondary endpoint: Endoscopic normalization at Week 12 | Comparison groups | Guselkumab 200 mg IV vs placebo |
| | | Adjusted treatment difference (95% CI) | 10.1% (5.9%, 14.3%) |
| | | Nominal P-value | <0.001 |

### *2.6.5.3. Clinical studies in special populations*

**Table 39: Number of Subjects by Age Group in Induction Study 1, Induction Study 2, and Maintenance Study; All Treated Analysis Set (Study CNTO1959UCO3001)**

| | | Age Group | |
|---|---|---|---|
| | Overall | 65 - 74 Years | 75 - 84 Years |
| Induction Studies | | | |
| Induction Study 1 | 327 | 14 (4.3%) | 7 (2.1%) |
| Induction Study 2 | 735 | 40 (5.4%) | 4 (0.5%) |
| Total | 1062 | 54 (5.1%) | 11 (1.0%) |
| Maintenance Study | | | |
| Randomized | 599 | 30 (5.0%) | 8 (1.3%) |
| Nonrandomized | 247 | 14 (5.7%) | 0 |
| Total | 846 | 44 (5.2%) | 8 (0.9%) |

Note: Includes all treated subjects (regardless of modified Mayo score at induction baseline).

#### *2.6.5.4. In vitro biomarker test for patient selection for efficacy*

Not applicable.

#### *2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable.

#### *2.6.5.6. Supportive study - Study CNTO1959UCO2002 (Study VEGA)*

Study Vega is a double-blind, controlled, proof-of-concept trial at 54 hospitals, academic medical centres, or private practices in nine countries. Eligible adults (aged ≥18 to 65 years) had a confirmed diagnosis of ulcerative colitis at least 3 months before screening and moderately-to-severely active ulcerative colitis (Mayo score 6–12) with a centrally-read baseline endoscopy subscore of 2 or higher. Patients were randomly assigned (1:1:1) using a computer-generated randomisation schedule to combination therapy (subcutaneous golimumab 200 mg at week 0, subcutaneous golimumab 100 mg at weeks 2, 6, and 10, and intravenous guselkumab 200 mg at weeks 0, 4, and 8, followed by subcutaneous guselkumab monotherapy 100 mg every 8 weeks for 32 weeks), golimumab monotherapy (subcutaneous golimumab 200 mg at week 0 followed by subcutaneous golimumab 100 mg at week 2 and every 4 weeks thereafter for 34 weeks), or guselkumab monotherapy (intravenous guselkumab 200 mg at weeks 0, 4, and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks thereafter for 32 weeks). The primary endpoint was clinical response at week 12 (defined as a ≥ 30% decrease from baseline in the full Mayo score and a ≥3 points absolute reduction with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1). Efficacy was analysed in the modified intention-to-treat population up to week 38, which included all randomly assigned patients who received at least one (partial or complete) study intervention dose. Safety was analysed up to week 50, according to study intervention received among all patients who received at least one (partial or complete) dose of study intervention.

Between Nov 20, 2018, and Nov 15, 2021, 358 patients were screened for eligibility, of whom 214 patients were randomly assigned to combination therapy (n=71), golimumab monotherapy (n=72), or guselkumab monotherapy (n=71). Of the 214 patients included, 98 (46%) were women and 116 (54%) were men and the mean age was 38·4 years (SD 12·0).

Main clinical efficacy results were as follows:

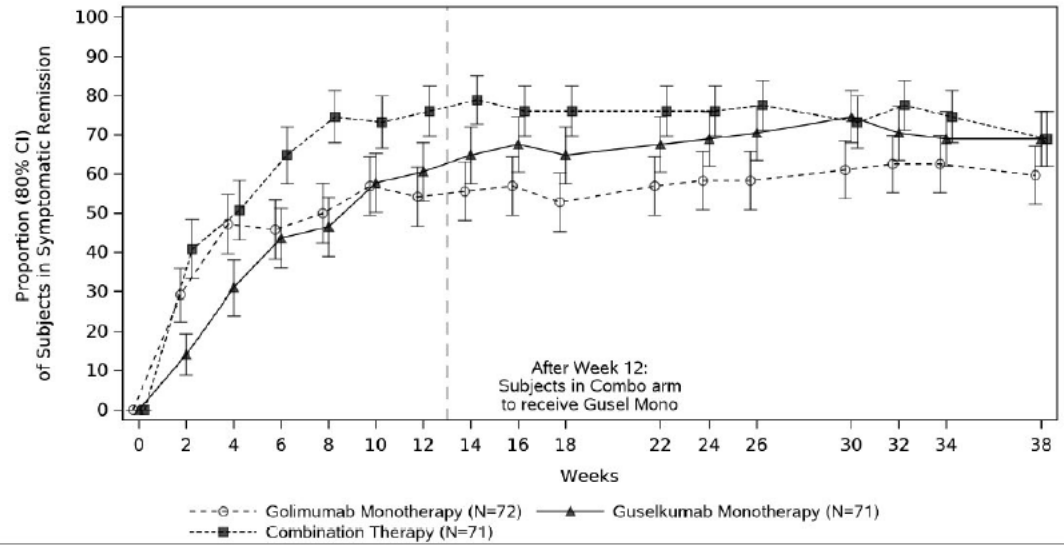
**Induction period**

**Table 40: Number of subjects who achieved clinical response at Week 12 based on the primary estimand (Estimad 1): primary analysis; full analysis set (Study CNTO1959UCO2002)**

| | Golimumab Monotherapy | Guselkumab Monotherapy | Combination Therapy |
|---|---|---|---|
| Analysis set: Full | 72 | 71 | 71 |
| Clinical response at Week 12 | | | |
| N | 72 | 71 | 71 |
| Subjects in clinical response[a,b,c] | 44 (61.1%) | 53 (74.6%) | 59 (83.1%) |
| 80% CI for rate[d] | (53.7%, 68.5%) | (68.0%, 81.3%) | (77.4%, 88.8%) |
| Adjusted treatment difference (80% CI)[e] | 22.1% (12.9%, 31.3%) | 8.5% (-0.2%, 17.1%) | |
| p-value[f] | 0.003 | 0.215 | |
| Clinical remission (legacy definition) at Week 12 | | | |
| N | 72 | 71 | 71 |
| Subjects in clinical remission (legacy definition)[a,b,c] | 16 (22.2%) | 15 (21.1%) | 26 (36.6%) |
| 80% CI for rate[d] | (15.9%, 28.5%) | (14.9%, 27.3%) | (29.3%, 43.9%) |
| Adjusted treatment difference (80% CI)[e] | 14.5% (4.9%, 24.0%) | 15.5% (6.0%, 25.0%) | |
| p-value[f] | 0.058 | 0.041 | |

**Maintenance period**

**Figure 42: Line plots of proportion of subjects in symptomatic remission by Visit through Week 38; full analysis set (Study CNTO1959UCO2002)**




## 2.6.6. Discussion on clinical efficacy

The efficacy for guselkumab in UC is based on data from 2 Phase 3 studies (Induction Study 2 (IS-2) and Maintenance Study (M)) and supported by a Phase 2b induction dose-ranging study (Induction Study 1; IS-1) conducted under a single protocol, CNTO1959UCO3001 (QUASAR). All 3 QUASAR studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of guselkumab in adults with moderately to severely active UC with a history of an inadequate response or failure to tolerate conventional (ie, 6-MP, AZA, or corticosteroids) or ADT (ie, TNF antagonists, vedolizumab, or tofacitinib). These studies provide information on 56

weeks (12 weeks of IV induction + 44 weeks of SC maintenance) of guselkumab treatment experience. Long-term extension of the QUASAR-M study is ongoing.

Results from the VEGA study which evaluated the efficacy and safety of the 12 weeks treatment with a combination of guselkumab and golimumab, followed by a transition to guselkumab monotherapy (26 weeks), versus each monotherapy, in participants with moderately to severely active UC were submitted. However, at the moment, a positive benefit-risk ratio of guselkumab-golimumab combination therapy in the induction phase cannot not be established, these results are only as supportive safety data.

**Dose finding induction study - QUASAR IS-1**

In Study IS-1, primary efficacy endpoint was the clinical response at Week I-12. The choice of this endpoint which is more sensitive for dose selection compared to the clinical remission rate endpoint used in Study IS-2 was found appropriate by the CHMP.

The rationale of induction dose selection for Study IS-1 in participants with UC was based on the similar dose regimen in CD and UC for ustekinumab, an approved IL-12/23 antagonist. Therefore, since the 200 mg IV induction regimen showed efficacy in the guselkumab Phase 2 CD study and was selected for confirmatory evaluation in the guselkumab Phase 3 CD studies, it was also considered appropriate to study in UC. Compared with CD, UC may need a higher induction dose, as patients with UC may have a higher inflammatory burden. Therefore, 200mg and 400 mg guselkumab IV induction dose regimens were included in the Study IS-1. This is agreed by the CHMP.

Only the primary clinical efficacy endpoint was controlled for multiplicity in Study IS-1, therefore p values for secondary and other efficacy endpoints are nominal values. Primary efficacy endpoint was met in Study IS-1 for both 200mg and 400mg IV induction dose, since the difference in the clinical response rate of placebo and guselkumab groups at Week I-12 was significant. For primary and major secondary endpoints, clinical response rates in both guselkumab dose groups are rather similar; the same applies for major secondary endpoints. The 200mg IV induction dose was therefore chosen for the phase 3 clinical studies.

**Design and conduct of Phase 3 clinical studies**

*Phase 3 induction study QUASAR IS-2*

Inclusion and exclusion criteria of IS-2 study are acceptable to the CHMP and in line with the intended patient population. UC patients with modified Mayo score of 4 were also planned to be included and were randomised in the QUASAR studies. However, as already highligthed at the time of the Scientific Advice, the CHMP considered that such score would represent a mild disease. Therefore, while the study was ongoing, the MAH amended the protocol to include participants with moderately to severely active UC (baseline modified Mayo Score of 5 to 9) in the primary analysis population. Because the modified Mayo score of 4 population could have a clinically relevant level of disease activity based on the endoscopy and rectal bleeding subscore requirements, the MAH still permitted continued enrolment of a limited number of participants with a modified Mayo score of 4 (capped at ≤5% of the total population). The targeted enrolment for the programme was increased from approximately 950 to 1,000 participants. This population with a modified Mayo score of 4 at induction baseline was analysed separately and was not included in the primary efficacy and safety analysis. Since the proportion of patients with modified Mayo score of 4 was low (below 5%), the CHMP concluded that the exclusion of these clinical efficacy data from the primary analysis did not affect the appropriateness of the analysis. This was further supported by the sensitivity analysis. The CHMP agreed to include results in patients with a modified Mayo score of 4 in section 5.1 of the SmPC since this subgroup of patients has a clinically relevant level of disease activity based on the endoscopy (ES ≥2) and rectal bleeding subscore (RBS ≥1) requirements.

The study treatments in the IS-2 study were 200 mg guselkumab i.v. or placebo i.v. As indicated in the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1), placebo is an acceptable comparator for a second line indication (after failure or intolerance to primary therapy). Hence, since guselkumab is intended for use after failure or intolerance to either conventional therapy, or a biologic treatment, the CHMP agreed that an active control arm is not required in the induction and maintenance studies.

IS-1 and 2 Week 12 nonresponders had the possiblity to receive 3 additional doses of 200 mg i.v. or sc. guselkumab Q4W for placebo or guselkumab iv. patients, respectively.

IS-1/IS-2 Week 12 responders entered the QUASAR Maintenance study.

The primary objective of Study IS-2 was to evaluate the efficacy of guselkumab as induction therapy and also to evaluate the safety. Intercurrent events and the corresponding estimand strategies for the primary objective of Study IS-2 are acceptable to the CHMP.

The primary efficacy endpoint was clinical remission rate at Week I-12, where participants were considered to have achieved clinical remission if they fulfilled the clinical remission criteria based on the modified Mayo Score components. The choice of this primary endpoint which is more stringent compared to the clinical response rate used in IS-1 is agreed by the CHMP.

The major secondary endpoints at Week 12 were symptomatic remission, endoscopic healing, clinical response, symptomatic remission, IBDQ remission, histologic-endoscopic mucosal healing, fatigue response, symptomatic remission, endoscopic normalization. The same intercurrent events, intercurrent strategy, estimands and supplementary estimands were applied for the main secondary endpoints as for the primary endpoint. This is agreed by the CHMP.

Major protocol deviations (MPDs), close to 10%, occurred with similar frequencies in the placebo and 200 mg iv guselkumab groups. They were led by non-compliance with inclusion or exclusion criteria and „other" MPDs. Frequencies of „Other" MPDs were between 3-5%, hence, upon the CHMP's request, the MAH clarified that the MPD category "other" was led by the Deviation from approved Investigational Product Preparation Instructions process, missed PRO or laboratory assessments at scheduled visits and endoscopy not performed per protocol in the study population. Further, the MAH presented the exact cases of MPDs concerning the study entry criteria non-compliance. Upon review of the cases, the CHMP concluded that the inclusion of the patients in question was adequately justified or not expected to have an impact on the efficacy data. The MAH presented also a sensitivity analysis for the key efficacy endpoints in patients without MPD. Comparison of the clinical efficacy outcomes on the primary and key secondary endpoints obtained for the full analysis set and for the patient population without any MPDs showed similar response rate results. The only slight exemption was the key secondary endpoint histologic mucosal healing at Week I-12, where the response rates in the guselkumab group were 8.0% and 7.5% for the sensitivity analysis population and for the full analysis set, respectively. The response rate on the above endpoint was 24.1% and 23.5% in the placebo groups for the sensitivity analysis population and for the full analysis set, respectively. However, these respective response rates are also considered rather similar. Therefore, the CHMP concluded that the primary and key secondary efficacy outcomes for the full analysis set and the sensitivity analysis population are similar. Summary of the AEs was also evaluated for the study population without MDPs and was found to be consistent with the findings in the population of the Safety dataset of IS-2. The MAH clarified that the number of study sites was rather high in the IS-2 part of the QUASAR programme, hence, the patient number at a certain site was rather low for the majority of study sites. There were few exceptions, where the patient number at the study sites was between 10 and 15, and in these sites few MPDs were reported. Therefore, MPDs are not attributed to specific study site(s). Overall, the CHMP concluded that MPD reported in the QUASAR programme are not expected to affect the study results.

The different analysis sets (full, efficacy all treated and Week I-12 Clinical Non-responder) for the efficacy analysis provided in the statistical analysis plan (SAP) are acceptable to the CHMP. Statistical analysis methods were defined for continuous and categorical (dichotomic) variables. Subgroups analyses were prespecified for region, demography characteristics, UC-related disease characteristics and UC-related previous and concomitant medication. The MAH established a fixed sequence testing procedure to control for multiplicity over the primary and major secondary endpoints at the 2-sided 0.05 significance level. There was one significant amendment in the SAP to accommodate the inclusion of UC patients with modified Mayo scores between 5 and 9 (both inclusive) instead of the original range of 4-9. This is acceptable to the CHMP.

*Maintenance study – QUASAR M*

The study population for the Phase 3 Maintenance Study included patients with clinical response at Week 12 or at Week 24 from IS-1 and IS-2. For these patients, a re-randomisation took place at the start of the maintenance study to placebo, 100 mg sc. guselkumab Q8W or 200 mg sc. guselkumab Q4W. In case of loss of clinical response, switch to 200 mg guselkumab Q4W was possible per protocol.

Patients reaching clinical response at Week 24 formed the non-randomised patient group in the maintenance study.

Estimands, clinical efficacy endpoints, and statistical analysis methods were similar as in Study IS-2, except for the timepoint since primary and key secondary efficacy endpoints were assessed at Week M-44 in the maintenance Study. One additional intercurrent event referring for guselumab dose adjustment was added to the estimand strategy of the maintenance study.

Similarly to Study IS-2, a fixed sequence testing of primary and main secondary efficacy endpoints was established for multiplicity control in the SAP. The CHMP noted that the hierarchical testing strategy for the maintenance Study does not adequately control the type 1 error rate. However, since the results for this study are significant with $p < 0.001$ for all considered endpoints except for the 7th major endpoint fatigue response at 200 mg SC q4w arm ($p < 0.01$) and the 8th major secondary endpoint maintenance of clinical remission in 100 mg SC q8w arm ($p<0.01$), the CHMP considered that other testing strategy controlling type I error would not have resulted in a different conclusion of this study.

PROMIS-29 and PROMIS Fatigue SF-7a were included as HRQoL measures in guselkumab IBD clinical studies. Validation reports of these PROs were provided. The Applicant 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.

**Efficacy data and additional analysis**

*Phase 3 induction study QUASAR IS-2*

Overall, 59 patients (8.0% of the randomised patients) of the Study IS-2 terminated the study without safety follow-up. From the patients in the Placebo and the Guselkumab groups who received additional induction treatment, 73 patients did not enter the maintenance study. However, this was not raised as a concern since the maintenance study included also patients from the dose finding induction study IS-1.

The population in the QUASAR studies were overall well balanced across the studies and the treatment arms with only few exception by baseline demography and UC-related characteristics.

The primary efficacy endpoint in Study IS-2 was met, since guselkumab 200 mg IV induction resulted in statistically significant difference in clinical remission rate compared with placebo ($p<0.001$).

Guselkumab 200 mg IV induction also resulted in significantly higher proportions of participants who achieved the major secondary endpoints ($p<0.001$) except for symptomatic remission at Week I-2 (not significant; $p=0.210$) and endoscopic normalization at Week I 12 (nominal $p<0.001$ based on the testing hierarchy).

The results on some endoscopic and histologic response rate endpoints not included among the key secondary endpoints of the IS-2 study are considered clinically relevant by the CHMP, while acknowledging that the p values were nominal.

Mayo score related continuous (Mayo score, partial and modified Mayo scores) and dichotomous (response rates in stool frequency and rectal bleeding subscores) scores also showed differences between the placebo and guselkumab group as early as Week I-4. The CHMP acknowledged that all corresponding p-values were nominal.

The PROs results on the fatigue response and the IBDQ remission rate showed significant difference between the placebo and the guselkumab groups, and other response rate-type measures such as abdominal pain or bowel urgency severity or its impact showed also differences. The MAH acknowledged that a ≥7-point improvement was used for all 3 PROMIS measures (PROMIS-Fatigue SF-7a, PROMIS-29 PCS and PROMIS-29 MCS) to define clinically meaningful changes, although the validation study showed a slightly lower cutoff for PROMIS-29 PCS (≥6-points 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 above thresholds established for within-patient clinically meaningful changes. However, within-patient clinically meaningful changes cannot be applied to between-group comparisons.

The CHMP highlighted that, to be included in SmPC Section 5.1, QoL outcomes should be statistically significant and the treatment difference clinically relevant compared to placebo in line with the UC approval of other biologicals. PROMIS-Fatigue response and IBDQ remission at Week 12 were key secondary efficacy endpoints in the QUASAR programme, under Type I error control. For both endpoints, the difference between the guselkumab 200 mg IV group and the placebo IV group was statistically significant and considered clinically relevant. These improvements were also found to be clinically significant at Week 44. Therefore, the CHMP agreed with the inclusion of fatigue response, IBDQ remisision, total score and score domains (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function) in the SmPC Section 5.1.

PROMIS-29 measures were not under Type-I error control, therefore the respective p-values are nominal. Furthermore, at Week I-12, the adjusted treatment differences of the proportion of participants with a ≥9-point improvement from baseline in each of the 7 PROMIS-29 domain T-scores was considered borderline for depression, physical function, pain interference. Hence, the CHMP did not agree with the inclusion of PROMIS-29 in the SmPC Section 5.1.

Comparison of the Week I-24 response rates in the Week-12 non-responder subpopulation showed different outcome for the placebo non-responder and the guselkumab non-responder groups. Whereas patients in the placebo group, who were non-responders at Week I-12 appear to reach the Week I-12 response rates of the guselkumab group, the Week-12 non-responder patients of the guselkumab group showed lower response rates at Week-24 compared to the Week-12 response rate in the Guselkumab group. Upon the CHMP's request, the MAH provided, for the Week-12 non-responder subpopulation, the Week-24 key clinical efficacy results for the ADT-failed and the ADT-nonfailed subgroups in the Placebo-Guselkumab iv. switched patients and in the Guselkumab iv – guselkumab sc. switched patients:

- ADT non-failed patients achieved higher response rates at key efficacy endpoints compared to the ADT failed patients in the Placebo IV → Guselkumab 200 mg IV treatment group.
- In the Guselkumab 200 mg IV → Guselkumab 200 mg SC patient population, ADT non-failed patients achieved higher response rates at key efficacy endpoints compared to the ADT failed patients.
- Comparison with a certain prior ADT status (ADT-nonfailed or ADT-failed subpopulation) shows higher response rates at Week 24 in the respective Placebo IV → Guselkumab 200 mg IV treatment group compared to the Guselkumab 200 mg IV → Guselkumab 200 mg SC treatment group. This phenomenon is especially remarkable in the Guselkumab 200 mg IV → Guselkumab 200 mg SC treatment group of the ADT-failed subpopulation.

The above analyses are limited by the low number of patients and do not allow to draw firm conclusion on the continuation of treatment in ADT-failed patients non-responders at Week 12 weeks. Furthermore, longer term efficacy results need to be considered, as discussed in the QUASAR maintenance section.

*QUASAR Maintenance*

From the randomised and treated participants with modified Mayo score of 5-9, 478 patients entered in the Maintenance part of the QUASAR programme.

The population of QUASAR Maintenance study was overall considered by the CHMP balanced between the treatment arms for demography characteristics despite some differences. Indeed, in the randomised placebo group, there was a higher proportion of patients from Eastern Europe, in the non-randomised Week-24 sc. guselkumab responders lower proportion of white patients, and the highest proportion of Asian patients can be found.

The maintenance baseline disease characteristics indicate that the highest remaining disease burden (higher Mayo scores, higher concentration of intestine inflammatory biomarkers, lowest remission and response rates) was in the non-randomised guselkumab Week I-24 responder subpopulation despite the fact that these patients had already received six induction doses of 200 mg guselkumab each (three i.v. and then three s.c. doses). This might be indicative for a more treatment-refractory patient subpopulation.

Clinical efficacy response rates on the primary and most of the major secondary endpoints were similar or slightly higher at Week M-44 in the 200 mg sc Guselkumab Q4W group than in the 100 mg sc. guselkumab Q8W group. Response rates in both guselkumab groups were significantly higher compared to the placebo group. In addition, treatment with both guselkumab maintenance doses sustained clinically meaningful improvements for other endoscopic and histologic endpoints, symptomatic remission, inflammatory biomarker, and PRO endpoints. These results provide support of the efficacy of guselkumab maintenance 100mg s.c. q8w and for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgment, to consider a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w). Tretament discontinuation should be considered in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.

Among the participants who were in clinical response following guselkumab IV induction, a slight decline in the proportions of participants in symptomatic remission through Week M 44 was observed in both guselkumab treatment groups. Participants in the placebo group lost clinical benefit and a fall of the response rate was observed over time.

Both guselkumab maintenance dose regimens were efficacious in sustaining reductions of inflammatory biomarker concentrations for serum CRP and fecal calprotectin at maintenance baseline through Week M 44, while concentrations increased in the placebo group.

Week M-44 results on the PROs were inconclusive in the two guselkumab groups, since numerically better outcomes were achieved for half of the endpoints in the 100 and 200 mg doses, respectively. In case of fatigue response and IBDQ remission rate, the differences between the placebo and guselkumab arms were statistically significant, all other p values were nominal.

Because of the  slight decline of efficacy in the guselkumab groups through Week 44 of the maintenance study, the CHMP raised a concern on the long-term maintenance of efficacy. Upon the CHMP's request, the MAH clarified that longer term efficacy data are not available yet for the QUASAR programme. Instead, the MAH presented data showing sustained clinical efficacy on several endpoints including symptomatic remission, durable symptomatic remission and the more stringent deep symptomatic remission over time (requiring a Mayo rectal bleeding subscore of 0 and a Mayo stool frequency subscore of 0). Additionally, in the more refractory non-randomized group of guselkumab induction 24 week responders who had guselkumab exposure up to 68 weeks by Week M-44, symptomatic remission was sustained through Week M 44 and regardless of the ADT-failure status. The MAH has committed to provide the efficacy results of the QUASAR Maintenance study, when available. The issue was not further pursued by the CHMP.

The clinical benefits of guselkumab 200 mg SC q4w maintenance at Week M 44 in the guselkumab Week I-24 responders were lower by 15-20% for the majority of the endpoints than the Week M-44 results for participants randomized to the guselkumab 200 mg SC q4w group in the Maintenance Study. This suggests that this population has more recalcitrant disease. Upon the CHMP's request, the MAH provided the key efficacy outcomes at Week M-44 for the induction guselkumab 24-week responders based on ADT failure status. At week 44, lower response rates in the ADT-failed guselkumab induction Week-24 responder population were observed compared to the ADT naive population, as it was observed at Week I-24. Increases in the response rates were observed for both ADT status from Week I-24 to Week M-44. However, the CHMP acknowledged the limitations of these post-hoc analyses due to the low patient number, the lack of placebo control for Non-responder population in the maintenance part of QUASAR programme, hence, no dose recommendation is made.

Avoidance of corticosteroids is an important patient- and physician-preferred treatment goal for managing UC in clinical practice due to systemic toxicities and long-term side effects including bone loss and risk of osteoporosis, glaucoma, increased risk of diabetes and cardiovascular diseases, thromboembolism, poor wound healing, and increased risk of mortality (George 2020[40]). Almost 40% of participants were receiving oral corticosteroids upon entry into the Maintenance Study. Guselkumab maintenance treatment sustained clinically meaningful efficacy in the absence of concomitant corticosteroid use.

Prespecified subgroup analyses conducted on ADT-failure status, baseline clinical status, guselkumab induction dose received, inflammatory biomarker thresholds, and baseline body weight for key efficacy endpoints including primary, major secondary, and other selected histologic and endoscopic efficacy endpoints were generally consistent with the results observed in the primary analysis population. The guselkumab induction dose received (400 mg IV or 200 mg IV) did not have an apparent effect on efficacy in the Maintenance Study.

Greater efficacy was observed in both guselkumab treatment groups compared with placebo for the primary and all major secondary endpoints at Week M 44 and other key endpoints at or through Week

[40] George, John, et al. "Corticosteroid-free remission vs overall remission in clinical trials of moderate–severe ulcerative colitis and Crohn's disease." *Inflammatory bowel diseases* 26.4 (2020): 515-523.

M 44 (including symptomatic remission over time) for the ADT naïve, ADT-nonfailure, and ADT failure subpopulations. Across all treatment groups, the proportions of participants who met the key endpoints were generally higher in the ADT-naïve and ADT-nonfailure subpopulations compared with the ADT-failure subpopulation. Time course of the key secondary endpoint symptomatic remission rate through Week M-44 by ADT failure status showed a more pronounced decline over time in the ADT failed subgroup than in the ADT-naive subgroup. Overall, the results for the ADT-nonfailure subpopulation are considered consistent with those for the ADT naïve subpopulation.

Guselkumab IV induction efficacy relative to placebo IV induction in participants with a modified Mayo score of 4 at induction baseline was consistent with the efficacy observed in the moderately to severely active UC population defined as a modified Mayo score of 5 to 9 at induction baseline. The clinical benefits of guselkumab maintenance compared with placebo at Week M 44 for participants with an induction baseline modified Mayo score of 4 were consistent with the primary analysis population of participants with a baseline modified Mayo score of 5 to 9.

**Therapeutic indication**

The MAH initially applied for the following indication: *Tremfya is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor.*

In the ADT-failed population of QUASAR study, almost 90% failed at least one TNF-alfa inhibitor, approximately half failed vedolizumab and about 20.0% failed tofacitinib. It is acknowledged that the proportions of patients in the induction studies and maintenance study who failed to respond to only vedolizumab treatment (6.8-9.9%) or only tofacitinib treatment (1.7-2.7%) are limited. However, considerable proportions of study patients who failed to respond to advanced treatment failed to respond to these and other treatments (vedolizumab: 49.2-54.1%, tofacitinib: 18-20.9%) and the clinical efficacy of guselkumab was also demonstrated in UC study patients who failed to respond to advanced treatment. This indirectly supports the clinical efficacy of guselkumab in UC patients who failed to respond to particular UC medicinal products. The CHMP agreed that results from failure to tofacitinib could be extrapolated to other medicinal products within the JAK inhibitor therapeutic class.

Furthermore, the CHMP noted that the subgroup analyses in patients who failed JAKis are limited to tofacitinib only in a few patients. Considering that conventional treatment or a biologic treatment includes the JAK inhibitors, upon the CHMP's request, the MAH agreed to remove *patients with inadequate or lost reponse or failure JAK inhibitors* in the wording of the indication.

Finally, the CHMP acknowledged that only few patients were in the "intolerance" subcategory. However, in line with the other biologics authorised in the UC indication, the CHMP agreed with an indication of patients whor are inadequate responders, lost response or are intolerant to conventional therapy or biologic treatment.

The following indication is agreed by the CHMP: *Tremfya is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment.* The pivotal study results are adequately described in section 5.1 of the SmPC to allow for an informed decision.

## 2.6.7. Conclusions on the clinical efficacy

The clinical efficacy data from the QUASAR programme demonstrate clinical efficacy for guselkumab during induction and maintenance phases in the treatment of patient with moderate to severe UC. The CHMP noted signs of a slight decline of guselkumab efficacy over time through Week M-44. However,

to conclude whether the trend is temporal or persistent, longer term efficacy data from the ongoing extension of the QUASAR programme are needed, the MAH has agreed to submit these data.

The following indication is agreed by the CHMP: *Tremfya is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment.*

The following posology is recommended: *The recommended induction dose is 200 mg administered by intravenous infusion at Week 0, Week 4 and Week 8. After completion of the induction dose regimen, 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 of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1).*

*Immunomodulators and/or corticosteroids may be continued during treatment with guselkumab. In patients who have responded to treatment with guselkumab, corticosteroids may be reduced or discontinued in accordance with standard of care.*

*Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.*

## 2.6.8. Clinical safety

The safety of guselkumab200 mg IV induction and guselkumab200 mg or 100 mg SC maintenance treatment in adult patients with moderately to severely active UC was evaluated in the CNTO1959UCO3001 (hereafter referred to as QUASAR) programme.

The QUASAR programme included 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter studies conducted under a single protocol. Supportive safety data are provided from a Phase 2a study in UC (CNTO1959UCO2002; hereafter referred to as VEGA), Phase 2 and Phase 3 studies in CD (CNTO1959CRD3001; [GALAXI 1, GALAXI 2, and GALAXI 3] and CNTO1959CRD3004 [GRAVITI]), and Phase 2 and Phase 3 studies in the approved indications of plaque psoriasis and PsA.

*Safety Analysis Sets*

- Safety Analysis Set: all randomized participants with a baseline modified Mayo Score of 5 to 9 who received at least 1 (partial or complete) dose of study intervention.
- Safety All Treated Analysis Set: all randomized participants (regardless of baseline modified Mayo Score) who received at least 1 (partial or complete) dose of study intervention.
- Week I-12 Clinical Nonresponder Safety Analysis Set: participants with a baseline modified Mayo Score of 5 to 9 who were not in clinical response at Week I-12 and received study intervention at Week I-12.

Participants were analyzed according to the study intervention they actually received.

Similar analysis sets were defined for PK and Immunogenicity analyses.

### *2.6.8.1. Patient exposure*

**Table 41: Summary of Guselkumab Exposure From Week 0 of Induction up to Approximately One Year Reporting Period; UC Maintenance Randomized Safety Analysis Set**

| | 100 mg SC q8w | 200 mg SC q4w | Combined |
|---|---|---|---|
| Analysis set: UC Maintenance Randomized Safety | 186 | 190 | 376 |
| Duration of guselkumab exposure | | | |
| At least 6 months[c] | 186 (100.0%) | 190 (100.0%) | 376 (100.0%) |
| At least 1 year[d] | 161 (86.6%) | 159 (83.7%) | 320 (85.1%) |
| Average duration of guselkumab treatment (weeks) | 44.7 | 47.2 | 46.0 |
| Total dose (mg) | | | |
| N | 186 | 190 | 376 |
| Mean (SD) | 1119.9 (233.84) | 2597.2 (601.30) | 1866.4 (869.59) |
| Median | 1100.0 | 2800.0 | 1600.0 |
| Range | (700; 1700) | (800; 3400) | (700; 3400) |
| IQ range | (1100.0; 1100.0) | (2800.0; 2800.0) | (1100.0; 2800.0) |

[a] Up to 56 weeks for subjects who entered the Maintenance Study at Week 12 of CNTO1959UCO3001 Induction Study 1 or Induction Study 2; up to 68 weeks for subjects who entered the Maintenance Study at Week 24 of CNTO1959UCO3001 Induction Study 1 or Induction Study 2.
[b] Includes data up to the time of dose adjustment for subjects who had a dose adjustment.
[c] The duration between the first and last guselkumab administration was at least 12 weeks.
[d] The duration between the first and last guselkumab administration was at least 36 weeks.
Note: CNTO1959UCO3001; Induction Study 1, Induction Study 2 and Maintenance Study.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline who were randomized in the Maintenance Study.
Note: Includes both IV and SC guselkumab doses.

### *2.6.8.2. Adverse events*

*Safety analysis sets*

**Table 42: QUASAR primary safety analysis sets**

| Analysis Set | N | Treatment Period | Study Population | Treatment Groups | Main Purpose |
|---|---|---|---|---|---|
| UC Induction Safety Analysis Set | 1,014 | Week I-0 to Week I-12 | Participants **with a modified Mayo score of 5 to 9** treated in QUASAR IS-1 or IS-2 | • Guselkumab 200 mg IV q4w x3<br>• Guselkumab 400 mg IV q4w x3<br>• Placebo | Primary safety assessment of guselkumab IV during a 12-week induction period |
| UC Maintenance Randomized Safety Analysis Set | 568 | Week M-0 to Week M-44 (primary analysis)<br><br>Week I-0 up to approximately 1-year reporting period (supportive analysis) | Participants **with a modified Mayo score of 5 to 9** who were guselkumab induction responders, randomized, and treated in the QUASAR Maintenance Study | • Guselkumab 200 mg SC q4w<br>• Guselkumab 100 mg SC q8w<br>• Placebo | Primary safety assessment of guselkumab SC during a 44-week maintenance period |

All AEs presented are treatment-emergent AEs (ie, any AEs occurring at or after the initial administration of study intervention in each respective study).

**Overall AE summary**

*QUASAR Induction pooled*

**Table 43: Overall Summary of Treatment-emergent Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12); UC Induction Safety Analysis Set**

| | | Guselkumab | | |
|---|---|---|---|---|
| | Placebo | 200 mg IV q4w | 400 mg IV q4w | Combined |
| Analysis set: UC Induction Safety | 385 | 522 | 107 | 629 |
| Average duration of follow-up (weeks) | 12.0 | 12.2 | 12.2 | 12.2 |
| Average exposure (number of administrations) | 2.9 | 2.9 | 3.0 | 2.9 |
| Subjects who died | 2 (0.5%) | 1 (0.2%) | 0 | 1 (0.2%) |
| Subjects with 1 or more: | | | | |
| Adverse events | 201 (52.2%) | 253 (48.5%) | 55 (51.4%) | 308 (49.0%) |
| Adverse events by maximum intensity[a] | | | | |
| Mild | 104 (27.0%) | 162 (31.0%) | 29 (27.1%) | 191 (30.4%) |
| Moderate | 72 (18.7%) | 78 (14.9%) | 22 (20.6%) | 100 (15.9%) |
| Severe | 25 (6.5%) | 13 (2.5%) | 4 (3.7%) | 17 (2.7%) |
| Serious adverse events | 26 (6.8%) | 13 (2.5%) | 3 (2.8%) | 16 (2.5%) |
| Adverse events leading to discontinuation of study agent | 14 (3.6%) | 8 (1.5%) | 0 | 8 (1.3%) |
| Infections[b] | 54 (14.0%) | 82 (15.7%) | 9 (8.4%) | 91 (14.5%) |
| Serious infections[b] | 1 (0.3%) | 3 (0.6%) | 0 | 3 (0.5%) |

[a] The maximum severity event of each subject is used.
[b] Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'.
Note: CNTO1959UCO3001; Induction Study 1 and Induction Study 2.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.

*QUASAR maintenance*

**Table 44: Overall Summary of TEAEs From Week M-0 Through Week M-44; UC Maintenance Randomized Safety Analysis Set (Study CNTO1959UCO3001; Maintenance)**

| | | Randomized Guselkumab (up to Dose Adjustment)[b] | | |
|---|---|---|---|---|
| | Randomized Placebo SC[a,b] | 100 mg SC q8w | 200 mg SC q4w | Combined |
| Analysis set: Randomized Safety | 192 | 186 | 190 | 376 |
| Average duration of follow-up (weeks) | 34.0 | 40.5 | 39.2 | 39.8 |
| Average exposure (number of administrations) | 8.2 | 9.9 | 9.6 | 9.8 |
| Subjects who died | 0 | 0 | 0 | 0 |
| Subjects with 1 or more: | | | | |
| AEs | 131 (68.2%) | 120 (64.5%) | 133 (70.0%) | 253 (67.3%) |
| AEs by maximum intensity: | | | | |
| Mild[c] | 57 (29.7%) | 61 (32.8%) | 73 (38.4%) | 134 (35.6%) |
| Moderate[d] | 69 (35.9%) | 49 (26.3%) | 54 (28.4%) | 103 (27.4%) |
| Severe[e] | 5 (2.6%) | 10 (5.4%) | 6 (3.2%) | 16 (4.3%) |
| SAEs | 1 (0.5%) | 5 (2.7%) | 12 (6.3%) | 17 (4.5%) |
| AEs leading to discontinuation of study agent | 13 (6.8%) | 7 (3.8%) | 5 (2.6%) | 12 (3.2%) |
| Infections[f] | 63 (32.8%) | 59 (31.7%) | 59 (31.1%) | 118 (31.4%) |
| Serious infections[f] | 0 | 1 (0.5%) | 2 (1.1%) | 3 (0.8%) |

| | Randomized Placebo SC[a,b] | Randomized Guselkumab (up to Dose Adjustment)[b] 100 mg SC q8w | 200 mg SC q4w | Combined |
|---|---|---|---|---|

3. [a] Subjects who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into this Maintenance Study.
4. [b] Includes data from Week M-0 up to the time of dose adjustment for subjects who had a dose adjustment or through Week M-44 for those who did not.
5. [c] Includes subjects with at least 1 AE, where all AEs are of mild intensity.
6. [d] Includes subjects with at least 1 AE of moderate intensity, and no AEs of severe intensity.
7. [e] Includes subjects with at least 1 AE of severe intensity.
8. [f] Infections were defined as any AE which was coded to the MedDRA SOC 'Infections and infestations'.
9. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.

**AEs by SOC and PT**

*QUASAR IS-1*

Adverse event frequencies by SOCs and the most frequently occurring PTs in QUASAR IS-1 induction study/Safety analysis set were as follows:

*Infections and infestations*

- Placebo: 10.5%, led by COVID-19 (3.8%) and Nasopharyngitis (1.9%) PTs
- Guselkumab 200 mg: 14.9%, lead by COVID-19 (5.9%) and Periodontitis (2.0%) PTs
- Guselkumab 400 mg: 8.4%, lead by COVID-19 (1.9%) PT

*Gastrointestinal disorders*

- Placebo: 18.1%, led by Colitis ulcerative (5.7%) PT
- Guselkumab 200 mg: 8.9%, lead by Abdominal pain (4.0%) and Diarrhoea (3.0%) PTs
- Guselkumab 400 mg: 11.2%, lead by Colitis ulcerative (3.7%) and Abdominal pain (2.8%) PTs

*Blood and lymphatic system disorders*

- Placebo: 14.3%, lead by Anaemia (9.5%) and Lymphopenia (4.8%) PTs
- Guselkumab 200 mg: 8.9%, lead by Anaemia (6.9%) PT
- Guselkumab 400 mg: 10.3%, lead by Anaemia (7.5%) PT

*Investigations*

- Placebo: 7.6%, led by Haemoglobine decreased (2.9%)
- Guselkumab 200 mg: 4.0%, led by AST (2.0%) and ALT (2.0%) increased PTs
- Guselkumab 400 mg: 10.3%, led by ALT increased (1.9%) and Neutrophil count decreased (1.9%) PTs

*Skin and subcutaneous system disorders*

- Placebo: 7.6%, led by Rash (1.9%) PT
- Guselkumab 200 mg: 6.9%, led by pruritus events (Pruritus and Rash pruritic PTs, 3.0% overall)
- Guselkumab 400 mg: 6.5%

*Muscoskeletal and connective tissue disorders*

- Placebo: 10.5%, led by Myalgia (2.9%) and Arthralgia (1.9%) PTs
- Guselkumab 200 mg: 4.0%, led by Arthralgia (2.0%) PT
- Guselkumab 400 mg: 7.5%, led by Arthralgia (3.7%) PT

*Nervous system disorders*

- Placebo: 10.5%, led by Headache PT (6.7%)
- Guselkumab 200 mg: 4.0%, led by Headache PT (3.0%)
- Guselkumab 400 mg: 7.5%, led by Headache PT (5.6%)

*Vascular disorders*

- Placebo: 2.9%
- Guselkumab 200 mg: 1.0%
- Guselkumab 400 mg: 2.8%, all of them were Hypertension PT

*Neoplasm benign, malignant and unspecified: 1 event in 1 patient in each treatment groups*

- Placebo: Skin haemangioma
- Guselkumab 200 mg: Colon adenoma
- Guselkumab 400 mg: Colon adenoma

*Hepatobiliary disorders*

Two events in two patients in the Guselkumab 200 mg group. No events in the Placebo and Guselkumab 400 mg groups.

*QUASAR IS-2*

*Infections and infestations*

- Placebo: 15.4%, led by COVID-19 (4.3%) and Nasopharyngitis (2.5%) PTs
- Guselkumab 200 mg: 15.7%, led by COVID-19 (5.0%), Nasopharyngitis (1.2%) and Influenza (1.2%) PTs

*Gastrointestinal disorders*

- Placebo: 17.5%, led by Colitis ulcerative (8.2%) and Nausea (2.5%) PTs
- Guselkumab 200 mg: 10.9%, led by Colitis ulcerative (2.4%) and Nausea (1.2%) PTs

*Skin and subcutaneous tissue disorder*

- Placebo: 3.9%, led by Rash (1.4%) PT
- Guselkumab 200 mg: 8.6%, led by Rash (2.1%), Pruritus-related events (2.1% overall)

*Blood and lymphatic system disorders*

- Placebo: 9.6%, led by Anaemia-related events (Anaemia+IDA - 7.5% overall) and Lymphopenia (1.4%) PTs
- Guselkumab 200 mg: led by Anaemia-related events (Anaemia+IDA - 5.9% overall)

*Investigations*

- Placebo: 5.4%, led by Haemoglobin decreased (1.4%) PT
- Guselkumab 200 mg: 8.1%, led by Haemoglobin decreased (2.1%), and WBC count decreased (1.7%) PTs

*Muscoskeletal and connective tissue disorders*

- Placebo: 3.2%, led by Arthralgia (2.1%) PT
- Guselkumab 200 mg: 4.5%, led by Arthralgia (1.4%) PT

*Nervous system disorders*

- Placebo: 4.6%, led by Headache (2.9%) PT
- Guselkumab 200 mg: 5.9%, led by Headache (3.1%) PT

*General disorders and administrative site conditions*

- Placebo: 3.6%, led by Pyrexia (1.1%) PT
- Guselkumab 200 mg: 3.8%, led by Pyrexia (1.7%) PT

*Vascular disorders*

- Placebo: 1.1%, led by Hypertension (0.7%) PT
- Guselkumab 200 mg: 1.7%, led by Hypertension (1.7%) PT

*Cardiac disorders*

- Placebo: 1.1% - 3 AEs, one of them a Cardiac arrest event

- Guselkumab 200 mg:0.7% - 3 AEs, two of them myocardial infarction events, under PTs Myocardial infarction and Acute myocardial infarction plus one Atrial fibrillation event

*Hepatobiliary disorders*

- Placebo: 0.4 % (1 patient)
- Guselkumab 200 mg: 0.7% (3 patients)

*Neoplasm benign, malignant and unspecified*

- Placebo: 0.4 % (1 patient)
- Guselkumab 200 mg: 0.7% (3 patients)

One pregnancy was reported during the Study IS-2 in a patient who was likely not exposed to guselkumab during her pregnancy, since her last menstruational period was at Day 28 of the study, and at the next visit urine h-CGT test already showed the pregnancy, therefore the study drug (guselkumab) was not administered at Week I-4. The narrative indicates that no protocol violation happened when this patient was included in the study, since she was not pregnant at the time of initial randomisation. However, contraceptive measures included in the inclusion criteria seem not to work fully appropriately in this case.

*QUASAR maintenance*

Treatment groups below are those after the Week M-0 re-randomisation of clinical responders at Week I-12.

*Infections and infestations*

- Placebo: 32.8%, led by COVID-19 (14.1%) and Upper respiratory tract infections (4.2%) PTs
- Guselkumab 100 mg Q8W: 31.7%, led by COVID-19 (12.9%) and Upper respiratory tract infections (3.2%) PTs
- Guselkumab 200 mg Q4W: 31.1%, led by COVID-19 (9.5%) and Upper respiratory tract infections (6.8%) PTs

*Gastrointestinal disorders*

- Placebo: 37.0%, led by Colitis ulcerative (29.7%) and Abdominal pain (2.1%) PTs
- Guselkumab 100 mg Q8W: 24.7%, led by Colitis ulcerative (9.1%) and Abdominal pain (2.7%) PTs
- Guselkumab 200 mg Q4W: 25.8%, led by Colitis ulcerative (13.2%) and Abdominal pain (3.7%) PTs

*Muscoskeletal and connective tissue disorders*

- Placebo: 11.5%, led by Arthralgia (6.8%) and back pain (2.6%) PTs
- Guselkumab 100 mg Q8W: 14.0%, led by Arthralgia (4.3%) and back pain (4.3%) PTs
- Guselkumab 200 mg Q4W: 15.3% led by Arthralgia (7.9%) and back pain (1.1%) PTs

*General disorders and administrative site conditions*

- Placebo: 8.3%, led by Pyrexia (2.6%) and Fatigue (3.1%) PTs
- Guselkumab 100 mg Q8W: 7.0%, led by Pyrexia (3.8%) PT
- Guselkumab 200 mg Q4W: 16.8%, led by Pyrexia (4.7%), and Injection site reaction (3.7%) PTs

*Skin and subcutaneous system disorders*

- Placebo: 5.7%, led by Rash (1.0%, 2 patients) PT
- Guselkumab 100 mg Q8W: 5.9%, led by Rash (1.6%, 3 patients) and Pruritus (1.1%, 2 patients) PTs
- Guselkumab 200 mg Q4W: 11.6% led by Rash (2.1%, 4 patients) and Pruritus (2.1%, 4 patients) PTs

*Nervous system disorders*

- Placebo: 7.8%, led by Headache (6.3%) PT
- Guselkumab 100 mg Q8W: 7.0% led by Headache (3.8%) PT
- Guselkumab 200 mg Q4W: 8.9% led by Headache (4.2%) PT

*Blood and lymphatic system disorders*

- Placebo: 6.8%, led by Anaemia (2.6%) PT
- Guselkumab 100 mg Q8W: 6.5% led by Anaemia (2.2%) PT
- Guselkumab 200 mg Q4W: 7.9% led by Anaemia (3.2%) PT

*Psychiatric disorders*

- Placebo: 2.1%
- Guselkumab 100 mg Q8W: 6.5%, led by Depression (2.7%) PT
- Guselkumab 200 mg Q4W: 3.7%

*Vascular disorders*

- Placebo: 3.6%, led by Hypertension (2.1%) PT
- Guselkumab 100 mg Q8W: 2.2%, led by Hypertension (1.6%, 3 patients) PT
- Guselkumab 200 mg Q4W: 4.2%, led by Hypertension (2.1%, 4 patients) PT

*Neoplasm benign, malignant and unspecified*

- Placebo: 2.6%
- Guselkumab 100 mg Q8W: 0.5%
- Guselkumab 200 mg Q4W: 2.1%

*Hepatobiliary disorders*

- Placebo: 0.5%
- Guselkumab 100 mg Q8W: 2.7%
- Guselkumab 200 mg Q4W: 1.1%

### *2.6.8.3. Serious adverse event/deaths/other significant events*

**Deaths**

*QUASAR IS-1 and IS-2 Pooled*

There were no deaths reported in QUASAR IS-1.

In QUASAR IS-2, 3 deaths were reported:

- One death in the 200 mg group at Study day 7 was due to fatal acute myocardial infarction in a participant with pre-existing cardiovascular risk factors (diabetes mellitus, hyperlipidaemia, extensive smoking history, coronary heart disease). The patient had received the first induction dose of IV guselkumab 200 mg on 13 Dec 2021 (Study Day 1 [Week I- 0]). She had no history of myocardial infarction, transient ischemic attack, or family history of early coronary artery disease or stroke. The investigator considered the event of acute myocardial infarction to be severe in intensity and not related to study intervention.
- Two deaths occurred in the placebo group (reported terms: natural causes and cardiac arrest).

*Maintenance*

During the QUASAR Maintenance Study, no deaths were reported through Week M-44.

**SAEs**

*Placebo-controlled Induction - QUASAR IS-1 and IS-2 Pooled*

The proportion of participants with 1 or more SAEs was numerically higher in the placebo group compared with the guselkumab groups:

- 2.5% of participants in the guselkumab 200 mg IV group.
- 2.8% of participants in the guselkumab 400 mg IV group.
- 6.8% of participants in the placebo IV group.

No PT was reported in more than 2 participants in the combined guselkumab group except for ulcerative colitis (n=7) and anemia (n=3).

The SOC with the highest overall frequencies of SAEs was Gastrointestinal disorders (8 [1.5%] participants in the 200 mg group, 1 [0.9%] participant in the 400 mg group, and 20 [5.2%] participants in the placebo group).

*Maintenance*

**Table 45: Number of Participants with Treatment-emergent SAEs Through Week M-44 Across Various Analysis Sets (Study CNTO1959UCO3001; Maintenance)**

| | Placebo | Guselkumab 100 mg SC q8w | Guselkumab 200 mg SC q4w |
|---|---|---|---|
| **UC Maintenance Randomized Safety Analysis Set[a,b]** | | | |
| **N** | 192 | 186 | 190 |
| **Subjects with 1 or more SAEs** | 1 (0.5%) | 5 (2.7%) | 12 (6.3%) |
| | | | |
| **UC Maintenance Nonrandomized Safety Analysis Set[c,d]** | | | |
| **N** | 114 | N/A | 123 |
| **Subjects with 1 or more SAEs** | 13 (11.4%) | N/A | 7 (5.7%) |
| | | | |
| **UC Maintenance Safety Analysis Set[e,f,g]** | | | |
| **N** | 296 | 186 | 401 |
| **Subjects with 1 or more SAEs** | 14 (4.7%) | 5 (2.7%) | 24 (6.0%) |
| | | | |
| **UC Maintenance All Treated Analysis Set[e,f,g]** | | | |
| **N** | 314 | 197 | 422 |
| **Subjects with 1 or more SAEs** | 15 (4.8%) | 5 (2.5%) | 24 (5.7%) |

[a] Placebo column includes subjects who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into the Maintenance Study.
[b] All columns include data from Week M-0 up to the time of dose adjustment for subjects who had a dose adjustment or through Week M-44 for those who did not.
[c] Placebo column includes subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the Maintenance Study. Includes data from Week M-0 through Week M-44.
[d] Guselkumab 200 mg SC q4w column includes subjects who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab from Week I-12. Includes data from Week M-0 through Week M-44.
[e] Placebo column includes 1) data from Week M-8 through Week M-44 for subjects who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into the Maintenance Study, up to the dose adjustment for subjects who had a dose adjustment; and 2) data from Week M-0 through Week M-44 for subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the Maintenance Study.
[f] Guselkumab 100 mg SC q8w column includes data from Week M-0 through Week M-44, or up to the dose adjustment for subjects who had a dose adjustment, for subjects who were in clinical response to guselkumab IV induction dosing and were randomized to guselkumab 100 mg SC q8w on entry into the Maintenance Study.
[g] Guselkumab 200 mg SC q4w column includes 1) subjects who were in clinical response to guselkumab IV induction dosing and were randomized to guselkumab 200 mg SC q4w on entry into the Maintenance Study, with data from Week M-0 through Week M-44; 2) subjects who were in clinical response to guselkumab IV induction dosing, randomized to placebo SC or guselkumab 100 mg SC q8w on entry into the Maintenance Study, and had a dose adjustment to guselkumab 200 mg SC q4w, with data from the time of dose adjustment through Week M-44; and 3) subjects who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab

from Week I-12 and received guselkumab 200 mg SC q4w on entry into the Maintenance Study, with data from Week M-0 through Week M-44.
Note: The UC Maintenance Randomized Safety Analysis Set, the UC Maintenance Nonrandomized Safety Analysis Set, and the UC Maintenance Safety Analysis Set include subjects with a modified Mayo score of 5 to 9 at induction baseline. The UC Maintenance All Treated Analysis Set includes subjects with a modified Mayo score of 4 to 9 at induction baseline

The overall proportions of participants with 1 or more SAEs through Week M-44 were low. The proportion of participants with SAEs was numerically higher in the guselkumab 200 mg SC q4w group compared with the placebo group:

- 6.3% of participants in the guselkumab 200 mg SC q4w group.
- 2.7% of participants in the guselkumab 100 mg SC q8w group.
- 0.5% of participants in the placebo SC group.

The SOC with the highest overall frequencies of SAEs was Gastrointestinal disorders (2 [1.1%] participants each in the guselkumab 200 mg group and the 100 mg group, and 1 [0.5%] participant in the placebo group). The SAEs reported in the guselkumab 200 mg group did not have a pattern with respect to individual PTs or SOCs, and the majority of these SAEs were assessed as unrelated to study intervention by the investigator. No PT was reported in more than 1 guselkumab-treated participant except for colitis ulcerative (n=2) and anxiety (n=2). A number of the reported PTs (including postoperative respiratory failure, rib fracture, cataracts, umbilical hernia, incisional hernia, and incarcerated incisional hernia) lacked biological plausibility for a causal relationship given the mechanism of action of guselkumab.

**Adverse Events of Special Interest**
AEs of special interest for the induction and maintenance studies under the CNTO1959UCO3001 protocol included malignancy and active tuberculosis.

*Malignancies*

*IS-1*

Through the final safety visit, there was 1 nonserious AE of basal cell carcinoma reported on Day 15 in the guselkumab 200 mg IV group. The participant had a medical history of basal cell carcinoma, but no basal cell carcinoma at the time of screening and randomization. There was no previous family history of basal cell carcinoma either. At the pre-planned annual dermatology examination, an excisional biopsy was performed to a skin nodule known to have existed before screening. The excised nodule was subsequently diagnosed as a basal cell carcinoma. Dermatologist proposed observation of the nodule and sun protection.

*IS-2*

One event of squamous cell carcinoma was reported on Day 23 in a participant with a past medical history of previously resected squamous cell carcinoma and concomitant corticosteroid use.

One event of basal cell carcinoma was reported on Day 32 in a participant with concomitant corticosteroid use. Both events occurred in the in the guselkumab 200 mg IV group.

*Maintenance*

Three participants had 4 malignancies of non-melanoma skin cancer. These participants were in the randomized placebo group of the QUASAR maintenance study.

- There was a female with no family history of basal cell carcinoma. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4

weeks and received the first induction dose of IV guselkumab (Study Day 1 [Week I-0]). At Week I-12, she achieved clinical response. She was assigned to receive SC placebo every 4 weeks in the Maintenance Study (first maintenance dose (Study Day 86 [Week M-0]). At (Study Day 290), a shave biopsy of right anterior shoulder lesion was carried out during the regular visit at dermatologist and pathology revealed superficial basal cell carcinoma with lateral margins involved. A non-serious adverse event of basal cell carcinoma was reported. No other treatment besides shave biopsy was received for this event. The investigator considered the event of basal cell carcinoma to be moderate in intensity, non-serious, and not related to study intervention. The investigator considered the event to be related to participant's age and sun-exposure.

- There was a female with a medical history of skin squamous cell carcinoma and family history of cancer in a 1st degree relative. She had routine skin surveillance visits with the dermatologist every 6 months and her skin was considered as sun damaged by the dermatologist due to the excessive sun exposure without sunscreen in childhood. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4 weeks. She was assigned to receive SC placebo every 4 weeks in the Maintenance Study and received first maintenance dose of SC placebo (Study Day 86 [Week M-0]). She met criteria for loss of clinical response and received SC guselkumab 200 mg every 4 weeks (Study Day 187 [Week M-16]).At induction week 12 visit, the participant reported that biopsies were performed on the lesions at different positions of the body and some of them confirmed the diagnosis squamous cell carcinoma. At Study Day 23, non-serious adverse events of squamous cell carcinoma of skin were reported. The investigator considered these events to be moderate in intensity and not related to study intervention.
- There was a female participant with no previous history of skin cancer or other malignancy but reported family medical history of possible skin cancer in close family members. She did not use sunscreen growing up. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4 weeks and received the first induction dose of IV guselkumab (Study Day 1 [Week I-0]). At Week I-12, she achieved clinical response. She was assigned to receive subcutaneous (SC) placebo every 4 weeks in the Maintenance Study and received first maintenance dose of SC placebo (Study Day 85 [Week M-0]). At Study Day 32, the participant had basal cell carcinoma confirmed by histopathology. The investigator considered the event of basal cell carcinoma to be moderate in intensity and not related to study intervention. At Study Day 370, a non-serious adverse event of basal cell carcinoma (reported term: right lower leg basal cell carcinoma ×2) was reported for the same patient and excision was performed and the event was considered resolved. The investigator considered this event to be mild in intensity, non-serious, and not related to study intervention.

Three participants had breast cancer (2 in the randomized placebo group and 1 in the non randomized placebo group).

- One participant was a female with no family history or known risk factors of breast cancer. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4 weeks and received the first induction dose of IV guselkumab (Study Day 1 [Week I-0]). At Week I-12, she achieved clinical response. She was assigned to receive subcutaneous (SC) placebo every 4 weeks in the Maintenance Study and received first maintenance dose of SC placebo (Study Day 87 [Week M-0]). A non-serious adverse event of breast cancer with onset at Study Day 129 was reported. The investigator considered the event of breast cancer to be moderate in intensity, non-serious, and not related to study

intervention. Treatment with study intervention was permanently discontinued due to the event of breast cancer. The event of breast cancer was reported as resolving.

- Breast cancer was reported in a female with medical history of ulcerative colitis, drug allergy, family history of cancer in a 1st degree relative, breast cancer. During the induction study, the patient received IV placebo, therefore the case is not further described.
- The third case was experienced by a patient who did not receive treatment with guselkumab.

One participant had clear cell renal cell carcinoma (nonrandomized guselkumab 200 mg SC q4w group). This patient was a male with medical history of ulcerative colitis and hypertension. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4 weeks and received the first induction dose of IV guselkumab (Study Day 1 [Week I-0]). At Week I-12, the patient was a non-responder to IV guselkumab induction dosing and received subcutaneous (SC) guselkumab 200 mg every 4 weeks starting on Study Day 81 [Week I-12]. At Week I-24, he achieved clinical response. He was assigned to receive SC guselkumab 200 mg every 4 weeks in the Maintenance Study and received first maintenance dose of SC guselkumab on Study Day 170 [Week M-0]. At Study Day 292, a CT scan of the abdomen was performed and revealed a "formation at the left kidney". The participant did not have symptoms of kidney disease. The investigator considered this event to be moderate in intensity and not related to study intervention. At Study Day 305, he underwent resection of the left kidney and histopathology report on Study Day 312, confirmed clear cell carcinoma of the left kidney. A serious adverse event of clear cell renal cell carcinoma was reported and was considered to be moderate in intensity and not related to study intervention by the investigator. Treatment with study intervention was permanently discontinued due to this event. At Study Day 315, the event of clear cell renal cell carcinoma was reported as resolved. The investigator confirmed that the participant did not receive any additional therapy for clear cell carcinoma of the kidney. In the opinion of the investigator, the event might have been related to genetic predisposition.

One participant had adenocarcinoma of the rectum (randomized guselkumab 200 mg SC q4w group). This patient was a female with medical history of extensive and long standing ulcerative colitis and depression. During the induction study, the participant was randomly assigned to receive intravenous (IV) guselkumab 200 mg every 4 weeks and received the first induction dose of IV guselkumab on Study Day 1 [Week I-0]. At Week I-12, she achieved clinical response. She was assigned to receive subcutaneous (SC) guselkumab 200 mg every 4 weeks in the Maintenance Study and received first maintenance dose of SC guselkumab on 1Study Day 85 [Week M-0]. The patient experienced a serious adverse event of abdominal pain on Study Day 247 and was hospitalized on the same day, the event was considered by the investigator as severe in intensity and not related to study intervention. The patient was thought to have met clinical flare and underwent endoscopy (sigmoidoscopy) to assess for loss of clinical response, where biopsy samples were collected. The histopathology showed grade 3 adenocarcinoma (rectal cancer without dissemination or metastasis) in the one sample, and adenocarcinoma tubulovillous with low grade dysplasia in the other sample. The investigator considered the event of adenocarcinoma to be severe in intensity and possibly related to study intervention. The event of abdominal pain was reported as resolved on Study Day 267. The event of adenocarcinoma was reported as resolving.

*Active TB*

No cases of active TB were reported during the induction and maintenance studies.

**Other Significant Adverse Events**

*Infections*

*QUASAR IS-1 and IS-2 Pooled*

The proportions of participants in the pooled guselkumab treatment groups who experienced 1 or more infections were as follows:

- 15.7% of participants in the guselkumab 200 mg IV group.
- 8.4% of participants in the guselkumab 400 mg IV group.
- 14.0% of participants in the placebo IV group.

The most common infection reported across all 3 treatment groups was COVID-19.

*Maintenance*

The proportions of participants with 1 or more infections through Week M-44 were as follows:

- 31.1% of participants in the guselkumab 200 mg SC q4w group.
- 31.7% of participants in the guselkumab 100 mg SC q8w group.
- 32.8% of participants in the placebo SC group.

The most common infection reported across all 3 treatment groups was COVID-19.

Most infections in the QUASAR programme were nonserious mild or moderate in intensity and did not result in discontinuation of study intervention.

*Serious infections*

*Induction studies*

The proportions of participants with 1 or more serious infections were as follows:

- Three (0.6%) participants in the guselkumab 200 mg IV group (reported PTs: Clostridium difficile infection [n=2] and staphylococcal sepsis [n=1]).
- No participants in the guselkumab 400 mg IV group.
- One (0.3%) participant in the placebo IV group (reported PT: appendicitis).

*Maintenance*

The proportions of participants with 1 or more serious infections were as follows:

- Two (1.1%) participants in the guselkumab 200 mg SC q4w group (reported PTs: bacterial infection [n=1] and complicated appendicitis [n=1]).
- One (0.5%) participant in the guselkumab 100 mg SC q8w group (reported PT: abscess).
- No participants in the placebo SC group.

*Opportunistic infections*

*QUASAR IS-1 and IS-2 Pooled*

There were no reports of opportunistic infections in QUASAR IS-1 through the final safety visit.

QUASAR IS-2:

- One patient in the placebo IV group
- One patient in the guselkumab 200 mg IV→guselkumab 200 mg SC group

The participant had chronic ongoing corticosteroid use through the final safety visit.

*Maintenance*

Among all treated participants in the QUASAR Maintenance Study, no cases of opportunistic infections were reported through Week M-44.

*Anaphylactic or Serum-Sickness Reactions*

There were no reports of anaphylaxis or serum sickness reactions in the QUASAR program through the Week M-44 visit.

*Cardiovascular Events (including MACE),*

*QUASAR IS-1 and IS-2 Pooled*

During the 12-week placebo-controlled induction period of the pooled QUASAR IS-1 and IS-2 studies, MACE were reported in 4 participants as follows:

- Two participants in the guselkumab 200 mg IV group in QUASAR IS-2 (1 nonfatal MACE [PT of myocardial infarction; pre-existing risk factors included hypertension, insulin dependent diabetes, chronic use of corticosteroids, and history of VTE] and 1 fatal MACE [PT of acute myocardial infarction; pre existing risk factors included: diabetes, hyperlipidemia, extensive smoking history, and a family history of coronary artery disease]).
- Two participants in the placebo group in QUASAR IS-2 (both fatal MACE [PTs of death and cardiac arrest]).

*Maintenance*

Through Week M-44, one MACE (haemorrhagic stroke) was reported in a participant in the UC Maintenance Randomized Safety Analysis Set who was randomized to guselkumab 200 mg SC q4w. The investigator reported advanced age () as a possible risk factor. The patient was an ex-smoker with history of chronic corticosteroid use.

There were no additional reports of MACE among all treated participants through Week M-44.

During the procedure, upon the CHMP's request, the MAH discussed MACE and other CV events observed in the QUASAR programme:

**Table 46: Number of Treatment-emergent MACE (Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke) per Hundred Subject-years of Follow-up Through Reporting Period with Data Beyond One Year by Category; SCS All Treated, Phase 2/3 Studies Analysis Set**

| | Ulcerative Colitis[a] | | Crohn's Disease[a] | | Inflammatory Bowel Disease[a] | | Psoriatic Diseases[a] | | All Diseases Pooled[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] |
| Analysis set: SCS All Treated, Phase 2/3 Studies | 546 | 968 | 340 | 1181 | 886 | 2149 | 885 | 3331 | 1771 | 5480 |
| Total subject-years of follow-up | 502.3 | 1421.9 | 205.6 | 2466.6 | 707.9 | 3888.5 | 334.0 | 9365.6 | 1041.9 | 13254.1 |
| MACE | | | | | | | | | | |
| Number of subjects with event | 4 (0.7%) | 5 (0.5%) | 0 | 3 (0.3%) | 4 (0.5%) | 8 (0.4%) | 1 (0.1%) | 30 (0.9%) | 5 (0.3%) | 38 (0.7%) |
| Number of events | 4 | 5 | 0 | 3 | 4 | 8 | 1 | 30 | 5 | 38 |
| Events per 100 subject-years | 0.80 | 0.35 | 0.00 | 0.12 | 0.57 | 0.21 | 0.30 | 0.32 | 0.48 | 0.29 |
| 95% CI[d] | (0.22, 2.04) | (0.11, 0.82) | (0.00, 1.46) | (0.03, 0.36) | (0.15, 1.45) | (0.09, 0.41) | (0.01, 1.67) | (0.22, 0.46) | (0.16, 1.12) | (0.20, 0.39) |
| Difference of event rate[e] | | -0.43 | | 0.08 | | -0.26 | | 0.02 | | -0.16 |
| 95% CI of difference[f] | | (-0.52, -0.35) | | (0.07, 0.09) | | (-0.32, -0.20) | | (-0.04, 0.07) | | (-0.20, -0.12) |
| Cardiovascular death | | | | | | | | | | |
| Number of subjects with event | 3 (0.5%) | 1 (0.1%) | 0 | 1 (0.1%) | 3 (0.3%) | 2 (0.1%) | 1 (0.1%) | 3 (0.1%) | 4 (0.2%) | 5 (0.1%) |
| Number of events | 3 | 1 | 0 | 1 | 3 | 2 | 1 | 3 | 4 | 5 |
| Events per 100 subject-years | 0.60 | 0.07 | 0.00 | 0.04 | 0.42 | 0.05 | 0.30 | 0.03 | 0.38 | 0.04 |
| 95% CI[d] | (0.12, 1.75) | (0.00, 0.39) | (0.00, 1.46) | (0.00, 0.23) | (0.09, 1.24) | (0.01, 0.19) | (0.01, 1.67) | (0.01, 0.09) | (0.10, 0.98) | (0.01, 0.09) |
| Difference of event rate[e] | | -0.52 | | 0.03 | | -0.34 | | -0.25 | | -0.31 |
| 95% CI of difference[f] | | (-0.59, -0.46) | | (0.02, 0.03) | | (-0.39, -0.30) | | (-0.30, -0.19) | | (-0.34, -0.27) |

**Number of Treatment-emergent MACE (Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke) per Hundred Subject-years of Follow-up Through Reporting Period with Data Beyond One Year by Category; SCS All Treated, Phase 2/3 Studies Analysis Set - continued**

| | Ulcerative Colitis[a] | | Crohn's Disease[a] | | Inflammatory Bowel Disease[a] | | Psoriatic Diseases[a] | | All Diseases Pooled[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] | Placebo[b] | Guselkumab [c] |
| Nonfatal myocardial infarction | | | | | | | | | | |
| Number of subjects with event | 1 (0.2%) | 2 (0.2%) | 0 | 1 (0.1%) | 1 (0.1%) | 3 (0.1%) | 0 | 21 (0.6%) | 1 (0.1%) | 24 (0.4%) |
| Number of events | 1 | 2 | 0 | 1 | 1 | 3 | 0 | 21 | 1 | 24 |
| Events per 100 subject-years | 0.20 | 0.14 | 0.00 | 0.04 | 0.14 | 0.08 | 0.00 | 0.22 | 0.10 | 0.18 |
| 95% CI[d] | (0.01, 1.11) | (0.02, 0.51) | (0.00, 1.46) | (0.00, 0.23) | (0.00, 0.79) | (0.02, 0.23) | (0.00, 0.90) | (0.14, 0.34) | (0.00, 0.53) | (0.12, 0.27) |
| Difference of event rate[e] | | -0.05 | | 0.03 | | -0.03 | | 0.18 | | 0.05 |
| 95% CI of difference[f] | | (-0.10, -0.01) | | (0.02, 0.03) | | (-0.06, 0.00) | | (0.17, 0.19) | | (0.03, 0.07) |
| Nonfatal stroke | | | | | | | | | | |
| Number of subjects with event | 0 | 2 (0.2%) | 0 | 1 (0.1%) | 0 | 3 (0.1%) | 0 | 6 (0.2%) | 0 | 9 (0.2%) |
| Number of events | 0 | 2 | 0 | 1 | 0 | 3 | 0 | 6 | 0 | 9 |
| Events per 100 subject-years | 0.00 | 0.14 | 0.00 | 0.04 | 0.00 | 0.08 | 0.00 | 0.06 | 0.00 | 0.07 |
| 95% CI[d] | (0.00, 0.60) | (0.02, 0.51) | (0.00, 1.46) | (0.00, 0.23) | (0.00, 0.42) | (0.02, 0.23) | (0.00, 0.90) | (0.02, 0.14) | (0.00, 0.29) | (0.03, 0.13) |
| Difference of event rate[e] | | 0.15 | | 0.03 | | 0.11 | | 0.08 | | 0.10 |
| 95% CI of difference[f] | | (0.13, 0.17) | | (0.03, 0.04) | | (0.09, 0.12) | | (0.08, 0.09) | | (0.09, 0.11) |

Key: MACE=major adverse cardiovascular event.
[a]Ulcerative colitis: CNTO1959UCO3001 (through January 31, 2024); CNTO1959UCO2002 through Week 38 (guselkumab monotherapy arm only); Crohn's disease: CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3,

and CNTO1959CRD3004 GRAVITI through May 15, 2024; Psoriasis: CNTO1959PSO3001 and CNTO1959PSO3002 through Week 264, CNTO1959PSO3003 through Week 60 and CNTO1959PSO2001 through Week 52; Psoriatic arthritis: CNTO1959PSA3001 through Week 60, CNTO1959PSA3002 through Week 112 and CNTO1959PSA2001 through Week 56.
[b]Ulcerative colitis: includes data up to the first dose of guselkumab for subjects who were initially treated with placebo; includes data at or after 12 weeks from the last induction dose of guselkumab for subjects who were treated with guselkumab in induction and were rerandomized to placebo in the Maintenance Study, up to the dose adjustment for subjects who had a dose adjustment. Crohn's disease and Psoriatic diseases: includes data up to the time of early escape/rescue or crossover.
[c]Ulcerative colitis: includes all guselkumab data and data up to 12 weeks from the last induction dose of guselkumab for subjects who were randomized to placebo in the Maintenance Study. Crohn's disease and Psoriatic diseases: includes data from the first dose of guselkumab onward for subjects who early escaped or crossed over from placebo.
[d]Confidence interval based on an exact method assuming that the observed number of events follows a Poisson distribution.
[e]For each disease, difference of incidence per 100 subject-years is calculated by subtracting the incidence of the compared drug (e.g. placebo) group from the incidence of the treatment group, weighted by total subject years of follow-up in the individual studies. Studies with no placebo arm, CNTO1959UCO2002 and CNTO1959PSO3003, are excluded from the derivation.
[f]Confidence interval based on normal approximation using Wald's method.
Note: Ulcerative colitis: CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study; CNTO1959UCO2002 (guselkumab monotherapy arm only); Crohn's disease: CNTO1959CRD3001 GALAXI 1, GALAXI 2 and GALAXI 3; CNTO1959CRD3004 GRAVITI; Psoriasis: CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003 and CNTO1959PSO2001; Psoriatic arthritis: CNTO1959PSA3001, CNTO1959PSA3002 and CNTO1959PSA2001.
Note: Includes all subjects who were treated.
Note: MACE were externally adjudicated in the plaque psoriasis program and underwent clinical review in other indications. Adverse events are coded using MedDRA Version 26.0.

*Venous Thromboembolism Events*

*Induction – QUASAR IS-1 and IS-2 Pooled*

There was 1 report of VTE in a participant treated with guselkumab 200 mg IV during the 12-week, placebo-controlled induction period of the QUASAR IS-1 study. The patient had multiple pre-existing risk factors, including prior VTEs. There were no additional reports of VTE through the final safety visit for QUASAR IS-1 and IS 2.

*Maintenance*

A VTE was reported in a participant in the UC Maintenance Randomized Safety Analysis Set with a history of prior VTE who was randomized to guselkumab 200 mg SC q4w

Through Week M-44, among all treated participants, an additional participant with a history of prior VTE in the nonrandomized guselkumab 200 mg SC q4w group reported VTEs (PTs: deep venous thrombosis and pulmonary embolism)

*Hepatic Disorders*

Clinically important hepatic disorder was defined as hepatic disorders reported as SAEs or hepatic AEs leading to discontinuation of study intervention. No clinically important hepatic disorders were reported during the QUASAR programme.

*QUASAR IS-1 and IS-2 Pooled*

The proportions of participants with (non-clinically important) hepatic disorder AEs during the 12-week placebo-controlled induction period of QUASAR IS-1 and IS-2 pooled is presented in Table 47.

**Table 47: Number of Subjects With 1 or More Treatment-emergent Hepatic Disorder Adverse Events During Placebo-controlled Induction Period (Week 0 to Week 12) by System Organ Class and Preferred Term; UC Induction Safety Analysis Set**

| | | Guselkumab | | |
|---|---|---|---|---|
| | Placebo | 200 mg IV q4w | 400 mg IV q4w | Combined |
| Analysis set: UC Induction Safety | 385 | 522 | 107 | 629 |
| Average duration of follow-up (weeks) | 12.0 | 12.2 | 12.2 | 12.2 |
| Average exposure (number of administrations) | 2.9 | 2.9 | 3.0 | 2.9 |
| Subjects with 1 or more hepatic disorder adverse events | 3 (0.8%) | 12 (2.3%) | 4 (3.7%) | 16 (2.5%) |
| System organ class<br>Preferred term | | | | |
| Investigations | 3 (0.8%) | 10 (1.9%) | 4 (3.7%) | 14 (2.2%) |
| Alanine aminotransferase increased | 1 (0.3%) | 4 (0.8%) | 2 (1.9%) | 6 (1.0%) |
| Aspartate aminotransferase increased | 0 | 4 (0.8%) | 1 (0.9%) | 5 (0.8%) |
| Gamma-glutamyltransferase increased | 2 (0.5%) | 5 (1.0%) | 0 | 5 (0.8%) |
| Blood bilirubin increased | 0 | 2 (0.4%) | 0 | 2 (0.3%) |
| Hepatic enzyme increased | 0 | 0 | 1 (0.9%) | 1 (0.2%) |
| Liver function test increased | 0 | 0 | 1 (0.9%) | 1 (0.2%) |
| Transaminases increased | 1 (0.3%) | 0 | 0 | 0 |
| Hepatobiliary disorders | 0 | 3 (0.6%) | 0 | 3 (0.5%) |
| Cholestasis | 0 | 2 (0.4%) | 0 | 2 (0.3%) |
| Hepatic function abnormal | 0 | 1 (0.2%) | 0 | 1 (0.2%) |

Note: CNTO1959UCO3001; Induction Study 1 and Induction Study 2.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
Note: Hepatic disorder adverse events are defined as the narrow terms in the MedDRA SMQ of 'Drug Related Hepatic Disorders - Comprehensive Search'. Adverse events are coded using MedDRA Version 26.0.

*Maintenance*

There were no clinically important hepatic events through Week M-44 in the QUASAR Maintenance Study.

Proportions of participants with hepatic disorders (UC Maintenance Randomized Safety Analysis Set) across the treatment groups is presented in Table 48.

**Table 48: Number of Participants With Treatment-emergent Hepatic Disorder AEs Through Week M-44 by SOC and PT; UC Maintenance Randomized Safety Analysis Set (Study CNTO1959UCO3001; Maintenance)**

| | | Randomized Guselkumab (up to Dose Adjustment)[b] | | |
|---|---|---|---|---|
| | Randomized Placebo SC[a,b] | 100 mg SC q8w | 200 mg SC q4w | Combined |
| Analysis set: Randomized Safety | 192 | 186 | 190 | 376 |
| Average duration of follow-up (weeks) | 34.0 | 40.5 | 39.2 | 39.8 |
| Average exposure (number of administrations) | 8.2 | 9.9 | 9.6 | 9.8 |
| Subjects with 1 or more hepatic disorder AEs | 4 (2.1%) | 10 (5.4%) | 4 (2.1%) | 14 (3.7%) |
| MedDRA SOC/PT | | | | |
| Investigations | 3 (1.6%) | 7 (3.8%) | 2 (1.1%) | 9 (2.4%) |
| Gamma-glutamyltransferase increased | 0 | 2 (1.1%) | 2 (1.1%) | 4 (1.1%) |
| Alanine aminotransferase increased | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| Aspartate aminotransferase increased | 1 (0.5%) | 0 | 1 (0.5%) | 1 (0.3%) |
| Blood bilirubin increased | 1 (0.5%) | 2 (1.1%) | 0 | 2 (0.5%) |
| Hepatic enzyme increased | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| Liver function test increased | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| Liver function test abnormal | 1 (0.5%) | 0 | 0 | 0 |
| Hepatobiliary disorders | 1 (0.5%) | 3 (1.6%) | 2 (1.1%) | 5 (1.3%) |
| Hepatic steatosis | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| Hepatic function abnormal | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| Hepatomegaly | 0 | 0 | 1 (0.5%) | 1 (0.3%) |
| Non-alcoholic steatohepatitis | 0 | 0 | 1 (0.5%) | 1 (0.3%) |
| Hyperbilirubinaemia | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| Hepatic cyst | 1 (0.5%) | 0 | 0 | 0 |

[a] Subjects who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into the Maintenance Study.
[b] Includes data from Week M-0 up to the time of dose adjustment for subjects who had a dose adjustment or through Week M-44 for those who did not.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
Note: Subjects are counted only once for any given event under a specific column, regardless of the number of times they actually experienced the event. AEs are coded using MedDRA Version 26.0.
Note: Hepatic disorder AEs are defined as the narrow terms in the MedDRA SMQ of 'DRUG RELATED HEPATIC DISORDERS - COMPREHENSIVE SEARCH'.
Note: A subject may appear in more than column/treatment group. A subject's exposure and AE data may be split across columns/treatment groups.

*Suicidal Ideation, Suicidal Behaviour, and Self-Injurious Behaviour.*

*Induction QUASAR IS-1 and IS-2*

- No guselkumab-treated participants had suicidal behaviour or self injurious behaviour without suicidal intent in IS-1 and IS-2 studies.
- Through Week I-12 in QUASAR IS-1, 2 (1.9%) participants in the guselkumab 400 mg IV group (1 of whom had a history of anxiety and depression) had suicidal ideation and 1 (1.0%) participant in the placebo IV group had self-injurious behaviour without suicidal intent.
- Through Week I-12 in QUASAR IS-2, 4 (1.0%) participants in the guselkumab 200 mg IV group (2 of whom had a history of anxiety and depression) and 2 (0.7%) participants in the placebo IV group had suicidal ideation.

*Maintenance, through Week M-44*

- 1 (0.5%) participant in the guselkumab 100 mg SC q8w group (with a history of depression) and 1 (0.5%) participant in the placebo SC group had suicidal ideation.
- 1 (0.5%) participant in the guselkumab 100 mg SC q8w group (with a history of depression) had suicidal behaviour.
- No participants reported self-injurious behaviour without suicidal intent.

Throughout the QUASAR programme, no participants reported a PT of completed suicide.

*Injections site reactions*

Through Week M-44 for the UC Maintenance Randomized Safety Analysis Set, the proportion of participants reporting injection-site reactions to guselkumab (up to dose adjustment) was 4.0%. Most injection-site reactions were mild. No injection-site reactions were SAEs, and none were severe AEs or led to discontinuation of study intervention. Injection-site reactions to guselkumab administration were reported by 7.9% of participants (2.5% of total injections received) in the guselkumab 200 mg SC q4w group and no participants in the guselkumab 100 mg SC q8w group.

The difference in the proportions of participants who had injection-site reactions between the 2 guselkumab groups may be related to the total number of injections containing active study intervention received by each (participants in the guselkumab 200 mg group received approximately 4 times as many as those in the 100 mg group). The most commonly reported PTs were injection site reaction, injection site pruritus, and injection site erythema.

Two (1.1%) participants (0.1% of injections) in the guselkumab 100 mg group and 2 (1.0%) participants (0.1% of injections) in the placebo group had injection-site reactions to placebo administration. The most commonly reported injection-site reaction to placebo was injection-site hematoma.

### *2.6.8.4. Laboratory findings*

**Haematology**

*Haemoglobin decreased*

Decreased haemoglobin levels (either at baseline or during the induction and maintenance studies) were common in the QUASAR studies. Shift of the haemoglobin level towards a more severe grade was also observed regardless the study treatment.

*Neutrophil count decreased*

*IS-1:*

- Placebo: 7.8%
- Guselkumab 200 mg: 14.0%
- Guselkumab 400 mg: 11.3%

*IS-2:*

- Placebo: 6.6%
- Guselkumab 200 mg: 9.0%

*Lymphocytes decreased*

*IS-1:*

- Placebo: 25.2%
- Guselkumab 200 mg: 21.0%
- Guselkumab 400 mg: 18.9%

*IS-2*

- Placebo: 18.3%
- Guselkumab 200 mg: 14.3%

**Clinical chemistry**

Presentation of clinical chemistry findings focuses on the liver function parameters.

**Table 49: Summary of Maximum Postbaseline ALT, AST, Total Bilirubin, and Alkaline Phosphatase Values During the Placebo-controlled Induction Period (Week 0 to Week 12); UC Induction Safety Analysis Set**

| | | Guselkumab | | |
|---|---|---|---|---|
| | Placebo | 200 mg IV q4w | 400 mg IV q4w | Combined |
| Analysis set: UC Induction Safety | 385 | 522 | 107 | 629 |
| Average duration of follow-up (weeks) | 12.0 | 12.2 | 12.2 | 12.2 |
| ALT | | | | |
| Participants with at least 1 postbaseline ALT value | 376 | 514 | 106 | 620 |
| Maximum postbaseline | | | | |
| ≤ULN | 356 (94.7%) | 488 (94.9%) | 98 (92.5%) | 586 (94.5%) |
| >ULN | 20 (5.3%) | 26 (5.1%) | 8 (7.5%) | 34 (5.5%) |
| >1 and <3 x ULN | 19 (5.1%) | 26 (5.1%) | 7 (6.6%) | 33 (5.3%) |
| ≥3 and <5 x ULN | 1 (0.3%) | 0 | 0 | 0 |
| ≥5 and <8 x ULN | 0 | 0 | 1 (0.9%) | 1 (0.2%) |
| ≥8 x ULN | 0 | 0 | 0 | 0 |
| AST | | | | |
| Participants with at least 1 postbaseline AST value | 376 | 514 | 106 | 620 |
| Maximum postbaseline | | | | |
| ≤ULN | 361 (96.0%) | 496 (96.5%) | 101 (95.3%) | 597 (96.3%) |
| >ULN | 15 (4.0%) | 18 (3.5%) | 5 (4.7%) | 23 (3.7%) |
| >1 and <3 x ULN | 15 (4.0%) | 18 (3.5%) | 5 (4.7%) | 23 (3.7%) |
| ≥3 and <5 x ULN | 0 | 0 | 0 | 0 |
| ≥5 and <8 x ULN | 0 | 0 | 0 | 0 |
| ≥8 x ULN | 0 | 0 | 0 | 0 |
| Total bilirubin | | | | |
| Participants with at least 1 postbaseline total bilirubin value | 375 | 514 | 106 | 620 |
| Maximum postbaseline | | | | |
| ≤ULN | 357 (95.2%) | 488 (94.9%) | 103 (97.2%) | 591 (95.3%) |
| >ULN | 18 (4.8%) | 26 (5.1%) | 3 (2.8%) | 29 (4.7%) |
| >1 and <2 x ULN | 15 (4.0%) | 26 (5.1%) | 3 (2.8%) | 29 (4.7%) |
| ≥2 x ULN | 3 (0.8%) | 0 | 0 | 0 |
| Alkaline Phosphatase | | | | |

| | Placebo | Guselkumab 200 mg IV q4w | Guselkumab 400 mg IV q4w | Guselkumab Combined |
|---|---|---|---|---|
| Participants with at least 1 postbaseline alkaline phosphatase value | 376 | 514 | 106 | 620 |
| Maximum postbaseline | | | | |
| ≤ULN | 347 (92.3%) | 459 (89.3%) | 98 (92.5%) | 557 (89.8%) |
| >ULN | 29 (7.7%) | 55 (10.7%) | 8 (7.5%) | 63 (10.2%) |
| >1 and <2 x ULN | 27 (7.2%) | 50 (9.7%) | 8 (7.5%) | 58 (9.4%) |
| ≥2 x ULN | 2 (0.5%) | 5 (1.0%) | 0 | 5 (0.8%) |
| >4 x ULN | 0 | 0 | 0 | 0 |

Note: CNTO1959UCO3001; IS-1 and IS-2.
Note: Includes only participants with modified Mayo score 5-9 at induction baseline.
Note: The maximum postbaseline value is used to determine the category.

In the QUASAR Maintenance Study:

- There were no cases meeting the biochemical criteria for Hy's law through Week M-44 in the UC Maintenance All Treated Analysis Set.
- Through Week M-44, in general, clinically meaningful effects of guselkumab on chemistry laboratory parameters were not observed.
- Through Week M-44, the proportions of participants with chemistry laboratory abnormalities by maximum postbaseline laboratory toxicity grades were generally similar among the guselkumab and placebo treatment groups.
- Through Week M-44, the majority (ie, ≥87.7%) of guselkumab-treated participants had maximum post-maintenance baseline ALT, AST, alkaline phosphatase, and total bilirubin levels that were within the reference range (≤1xULN). Most participants with abnormal post-maintenance baseline ALT, AST, alkaline phosphatase, or total bilirubin levels, had mild elevations (maximum ALT or AST <3xULN and alkaline phosphatase or total bilirubin <2xULN).

**Safety Update Report - CNTO1959UCO3001 (QUASAR) Maintenance Study**

Upon the CHMP's request, the MAH provided additional safety data available after Week M-44 through 31 January 2024 for the CNTO1959UCO3001 (QUASAR) Maintenance Study. This includes data from participants who were treated during the LTE of the Maintenance Study and data from participants who were followed for safety after Week M-44 but did not enter the LTE. No formal database lock has been performed for this Safety Update Report, and data collected after Week M-44 through 31 January 2024 in the QUASAR Maintenance Study have not been thoroughly cleaned and finalized. Data from Week M-0 through Week M-44 have been updated from those presented in the SCS to reflect the most current information in the safety database.

**Table 50: Treatment-emergent Serious Adverse Events From Week M-0 Through Week M-44 and After Week M-44 Through 31 January 2024; UC Maintenance Safety Analysis Set (Study CNTO1959UCO3001: Maintenance)**

| | Week M-0 Through Week M-44 | | | | After Week M-44 Through 31 January 2024 | | | |
|---|---|---|---|---|---|---|---|---|
| | | Guselkumab | | | | Guselkumab | | |
| | Combined Placebo SC[a] | 100 mg SC q8w[b] | 200 mg SC q4w[c] | Combined | Combined Placebo SC[d] | 100 mg SC q8w[e] | 200 mg SC q4w[f] | Combined |
| Analysis set: UC Maintenance Safety | 296 | 186 | 401 | 568 | 196 | 157 | 347 | 504 |
| Average duration of follow-up (weeks) | 32.3 | 40.5 | 38.5 | 40.4 | 48.8 | 60.5 | 56.7 | 57.9 |
| Average exposure (number of administrations) | 7.8 | 9.9 | 9.3 | 9.8 | 11.3 | 15.3 | 14.7 | 14.9 |
| Subjects with 1 or more serious adverse events | 14 (4.7%) | 5 (2.7%) | 25 (6.2%) | 30 (5.3%) | 18 (9.2%) | 6 (3.8%) | 23 (6.6%) | 29 (5.8%) |
| Number of subjects with serious adverse events per hundred subject-years of follow-up | 7.63 | 3.46 | 8.46 | 6.82 | 9.81 | 3.30 | 6.10 | 5.19 |
| 95% CI for event rate per hundred subject-years | (4.17, 12.81) | (1.12, 8.08) | (5.47, 12.48) | (4.60, 9.73) | (5.82, 15.51) | (1.21, 7.18) | (3.87, 9.16) | (3.48, 7.45) |
| Number of serious adverse events | 18 | 5 | 36 | 41 | 22 | 9 | 37 | 46 |
| Number of serious adverse events per hundred subject-years of follow-up | 9.81 | 3.46 | 12.18 | 9.32 | 12.00 | 4.95 | 9.82 | 8.23 |
| 95% CI for event rate per hundred subject-years | (5.82, 15.51) | (1.12, 8.08) | (8.53, 16.86) | (6.68, 12.64) | (7.52, 18.16) | (2.26, 9.39) | (6.91, 13.53) | (6.03, 10.98) |

Serious infections were infrequently reported in guselkumab-treated participants. With the exception of pneumonia (3 cases) and appendicitis (2 cases), all serious infections were single events without a clear pattern, and none led to study intervention interruption or discontinuation. No cases of active TB or opportunistic infections were reported.

UC was the most common AE leading to discontinuation of study intervention.

No deaths were reported in guselkumab-treated participants. One death case occurred, the concerned patient was on placebo at the time of death.

MACE was reported in 2 guselkumab-treated participants (1 acute coronary syndrome and 1 thrombotic cerebral infarction, both of them had predisposition to the MACE event (history of angina, MI, VTE among others)) and in 2 placebo patients, one of them had CV risk factors. VTE event occurred in two patients, both of them had previous VTE events prior entering the study.

There were no reports of anaphylaxis or serum sickness reactions.

There were no reports of clinically important hepatic disorders (ie, hepatic disorders reported as SAEs or AEs leading to discontinuation of study intervention).

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.

### *2.6.8.5. In vitro biomarker test for patient selection for safety*

Not applicable.

### *2.6.8.6. Safety in special populations*

**Intrinsic factors**

*Age*

**Table 51: Summary of Key Safety Events During the Maintenance Study Through Week M-44 by Age Group; UC Maintenance Randomized Safety Analysis Set (Study CNTO1959UCO3001; Maintenance)**

| | Age (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <65 | | 65 - 74 | | 75 - 84 | | ≥85 | |
| | Placebo [a] | Guselkumab [a] | Placebo [a] | Guselkumab [a] | Placebo [a] | Guselkumab [a] | Placebo [a] | Guselkumab [a] |
| Analysis set: UC Maintenance Randomized Safety | 180 | 353 | 10 | 18 | 2 | 5 | 0 | 0 |
| Average duration of follow-up (weeks) | 34.0 | 39.8 | 36.3 | 41.1 | 23.6 | 39.3 | - | - |
| Average duration of treatment (weeks) | 29.3 | 33.7 | 29.7 | 35.4 | 16.1 | 32.1 | - | - |
| Subjects with AEs | 119 (66.1%) | 235 (66.6%) | 10 (100.0%) | 13 (72.2%) | 2 (100.0%) | 5 (100.0%) | - | - |
| Serious AEs | | | | | | | | |
| Fatal | 0 | 0 | 0 | 0 | 0 | 0 | - | - |
| Hospitalization/prolong existing hospitalization | 0 | 14 (4.0%) | 0 | 1 (5.6%) | 1 (50.0%) | 2 (40.0%) | - | - |
| Life-threatening | 0 | 1 (0.3%) | 0 | 0 | 0 | 0 | - | - |
| Disability/incapacity | 0 | 1 (0.3%) | 0 | 0 | 0 | 0 | - | - |
| Other (medically important) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (20.0%) | - | - |
| Psychiatric disorders [b] | 4 (2.2%) | 18 (5.1%) | 0 | 1 (5.6%) | 0 | 0 | - | - |
| Nervous system disorders [b] | 13 (7.2%) | 28 (7.9%) | 2 (20.0%) | 2 (11.1%) | 0 | 0 | - | - |
| Accidents and injuries [c] | 8 (4.4%) | 15 (4.2%) | 0 | 1 (5.6%) | 0 | 1 (20.0%) | - | - |
| Cardiac disorders [b] | 1 (0.6%) | 5 (1.4%) | 0 | 0 | 0 | 1 (20.0%) | - | - |
| Vascular disorders [b] | 7 (3.9%) | 9 (2.5%) | 0 | 3 (16.7%) | 0 | 0 | - | - |
| Cerebrovascular disorders [d] | 0 | 0 | 0 | 1 (5.6%) | 0 | 0 | - | - |
| Infections and infestations [b] | 55 (30.6%) | 111 (31.4%) | 8 (80.0%) | 4 (22.2%) | 0 | 3 (60.0%) | - | - |
| Anticholinergic syndrome [e] | 0 | 0 | 0 | 0 | 0 | 0 | - | - |
| Quality of life decreased [e] | 0 | 0 | 0 | 0 | 0 | 0 | - | - |
| Sum of postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures [f] | 0 | 4 (1.1%) | 0 | 0 | 0 | 1 (20.0%) | - | - |

[a] Includes data up to the time of dose adjustment for subjects who had a dose adjustment.
[b] MedDRA system organ class.
[c] Accidents and injuries includes adverse events with a MedDRA high level group term (HLGT) of 'Bone and joint injuries', 'Injuries by physical agents', or 'Injuries NEC'.
[d] Cerebrovascular disorders includes adverse events with a MedDRA HLGT of 'Central nervous system vascular disorders'.
[e] MedDRA preferred term.
[f] Postural hypotension includes events with a MedDRA lower level term (LLT) of 'Postural hypotension', 'Hypotension postural', or 'Hypotension postural aggravated'. Fall includes events with a MedDRA LLT of 'Fall' or a MedDRA preferred term (PT) of 'Fall'. Black outs includes events with a MedDRA LLT of 'Blackout', 'Black-out (not amnesia)', 'Blacked-out (not amnesia)', 'Blacked out', or 'Blackout spell'. Syncope, dizziness and ataxia are MedDRA preferred terms. Fractures includes events with a MedDRA HLGT of 'Fractures' or a MedDRA PT of 'Fracture'.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline who were randomized in the Maintenance Study.

*Baseline demographic*

*Induction*

**Table 52: Overall Summary of Treatment-emergent Events During Placebo-controlled Induction Period (Week 0 to Week 12) by Baseline Demographic Factors; UC Induction Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 385 | 629 | | | | | | | | |
| Weight (kg, median) | <70.15 | 200 | 307 | 108 (54.0%) | 158 (51.5%) | 15 (7.5%) | 11 (3.6%) | 7 (3.5%) | 3 (1.0%) | 31 (15.5%) | 45 (14.7%) |
| | ≥70.15 | 185 | 322 | 93 (50.3%) | 150 (46.6%) | 11 (5.9%) | 5 (1.6%) | 7 (3.8%) | 5 (1.6%) | 23 (12.4%) | 46 (14.3%) |
| Age (years) | <65 years | 364 | 589 | 189 (51.9%) | 284 (48.2%) | 22 (6.0%) | 15 (2.5%) | 14 (3.8%) | 8 (1.4%) | 52 (14.3%) | 82 (13.9%) |
| | ≥65 years | 21 | 40 | 12 (57.1%) | 24 (60.0%) | 4 (19.0%) | 1 (2.5%) | 0 | 0 | 2 (9.5%) | 9 (22.5%) |
| Sex | Male | 227 | 357 | 112 (49.3%) | 157 (44.0%) | 12 (5.3%) | 8 (2.2%) | 7 (3.1%) | 6 (1.7%) | 24 (10.6%) | 41 (11.5%) |
| | Female | 158 | 272 | 89 (56.3%) | 151 (55.5%) | 14 (8.9%) | 8 (2.9%) | 7 (4.4%) | 2 (0.7%) | 30 (19.0%) | 50 (18.4%) |
| Race | White | 282 | 451 | 140 (49.6%) | 207 (45.9%) | 21 (7.4%) | 9 (2.0%) | 12 (4.3%) | 6 (1.3%) | 39 (13.8%) | 65 (14.4%) |
| | Black or African American | 4 | 6 | 2 (50.0%) | 4 (66.7%) | 0 | 1 (16.7%) | 0 | 0 | 0 | 2 (33.3%) |
| | Asian | 86 | 138 | 51 (59.3%) | 74 (53.6%) | 4 (4.7%) | 6 (4.3%) | 2 (2.3%) | 1 (0.7%) | 12 (14.0%) | 16 (11.6%) |
| | Other | 13 | 34 | 8 (61.5%) | 23 (67.6%) | 1 (7.7%) | 0 | 0 | 1 (2.9%) | 3 (23.1%) | 8 (23.5%) |
| Ethnicity | Hispanic or Latino | 25 | 34 | 14 (56.0%) | 20 (58.8%) | 3 (12.0%) | 1 (2.9%) | 1 (4.0%) | 2 (5.9%) | 6 (24.0%) | 6 (17.6%) |
| | Not Hispanic or Latino | 337 | 558 | 170 (50.4%) | 265 (47.5%) | 21 (6.2%) | 15 (2.7%) | 13 (3.9%) | 5 (0.9%) | 42 (12.5%) | 77 (13.8%) |
| | Not reported | 23 | 37 | 17 (73.9%) | 23 (62.2%) | 2 (8.7%) | 0 | 0 | 1 (2.7%) | 6 (26.1%) | 8 (21.6%) |

10. Note: CNTO1959UCO3001; IS-1 and IS-2.
11. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
12. Note: Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.

*Maintenance*

**Table 53: Overall Summary of Treatment-emergent Events per Hundred Subject-years of Follow-up During the Maintenance Study Through Week M-44 by Induction Baseline Demographic Factors; UC Maintenance Randomized Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 192 | 376 | | | | | | | | |
| Weight (kg, median) | <70 | 86 | 191 | 331.38 | 317.72 | 1.87 | 4.16 | 11.23 | 4.16 | 76.76 | 60.35 |
| | ≥70 | 106 | 185 | 256.77 | 272.80 | 0.00 | 12.59 | 9.77 | 4.20 | 57.21 | 65.75 |
| Age (years) | <65 years | 180 | 353 | 277.27 | 289.40 | 0.00 | 6.32 | 8.53 | 4.09 | 62.28 | 63.53 |
| | ≥65 years | 12 | 23 | 458.15 | 384.65 | 12.73 | 39.02 | 38.18 | 5.57 | 114.54 | 55.75 |
| Sex | Male | 110 | 201 | 220.50 | 245.52 | 1.31 | 5.28 | 6.56 | 2.64 | 52.50 | 56.76 |
| | Female | 82 | 175 | 394.81 | 351.04 | 0.00 | 11.80 | 16.37 | 5.90 | 85.92 | 70.06 |
| Race | White | 144 | 272 | 279.53 | 246.00 | 0.00 | 6.78 | 9.46 | 4.36 | 67.26 | 63.92 |
| | Black or African American | 2 | 4 | 94.62 | 711.99 | 0.00 | 0.00 | 0.00 | 0.00 | 94.62 | 71.20 |
| | Asian | 34 | 82 | 348.50 | 385.67 | 4.84 | 12.59 | 19.36 | 1.57 | 58.08 | 47.22 |
| | Other | 12 | 18 | 268.39 | 525.39 | 0.00 | 14.01 | 0.00 | 14.01 | 61.00 | 119.09 |
| Ethnicity | Hispanic or Latino | 7 | 21 | 477.29 | 320.12 | 0.00 | 6.28 | 0.00 | 6.28 | 75.36 | 62.77 |
| | Not Hispanic or Latino | 175 | 329 | 276.94 | 279.21 | 0.88 | 8.35 | 11.39 | 3.98 | 63.98 | 60.85 |
| | Not reported | 10 | 26 | 372.12 | 480.73 | 0.00 | 10.12 | 0.00 | 5.06 | 85.87 | 91.08 |

13. Note: CNTO1959UCO3001; IS-1 and IS-2; Includes data up to the time of dose adjustment for subjects who had a dose adjustment.
14. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
15. Note: Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.

*Baseline disease characteristics*

*Induction*

**Table 54: Overall Summary of Treatment-emergent Events During Placebo-controlled Induction Period (Week 0 to Week 12) by Baseline Disease Characteristics; UC Induction Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 385 | 629 | | | | | | | | |
| Duration of disease (years) | <2 | 78 | 115 | 38 (48.7%) | 54 (47.0%) | 5 (6.4%) | 4 (3.5%) | 4 (5.1%) | 1 (0.9%) | 9 (11.5%) | 13 (11.3%) |
| | ≥2 to ≤5 | 104 | 168 | 49 (47.1%) | 88 (52.4%) | 7 (6.7%) | 6 (3.6%) | 4 (3.8%) | 5 (3.0%) | 11 (10.6%) | 28 (16.7%) |
| | >5 to ≤10 | 110 | 177 | 61 (55.5%) | 88 (49.7%) | 7 (6.4%) | 3 (1.7%) | 5 (4.5%) | 0 | 22 (20.0%) | 27 (15.3%) |
| | >10 | 93 | 169 | 53 (57.0%) | 78 (46.2%) | 7 (7.5%) | 3 (1.8%) | 1 (1.1%) | 2 (1.2%) | 12 (12.9%) | 23 (13.6%) |
| Severity of disease | Moderate (modified Mayo score 5-6) | 138 | 206 | 74 (53.6%) | 104 (50.5%) | 7 (5.1%) | 1 (0.5%) | 3 (2.2%) | 3 (1.5%) | 23 (16.7%) | 36 (17.5%) |
| | Severe (modified Mayo score 7-9) | 247 | 423 | 127 (51.4%) | 204 (48.2%) | 19 (7.7%) | 15 (3.5%) | 11 (4.5%) | 5 (1.2%) | 31 (12.6%) | 55 (13.0%) |
| Extent of disease | Limited | 192 | 334 | 99 (51.6%) | 160 (47.9%) | 15 (7.8%) | 6 (1.8%) | 8 (4.2%) | 2 (0.6%) | 28 (14.6%) | 49 (14.7%) |
| | Extensive | 193 | 295 | 102 (52.8%) | 148 (50.2%) | 11 (5.7%) | 10 (3.4%) | 6 (3.1%) | 6 (2.0%) | 26 (13.5%) | 42 (14.2%) |
| Baseline Mayo endoscopy subscore | Moderate: subscore of 2 | 130 | 189 | 68 (52.3%) | 92 (48.7%) | 8 (6.2%) | 3 (1.6%) | 5 (3.8%) | 2 (1.1%) | 22 (16.9%) | 33 (17.5%) |
| | Severe: subscore of 3 | 255 | 440 | 133 (52.2%) | 216 (49.1%) | 18 (7.1%) | 13 (3.0%) | 9 (3.5%) | 6 (1.4%) | 32 (12.5%) | 58 (13.2%) |

16. Note: CNTO1959UCO3001; IS-1 and IS-2.
17. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
18. Note: Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.

*Maintenance*

**Table 55: Overall Summary of Treatment-emergent Events per Hundred Subject-years of Follow-up During the Maintenance Study Through Week M-44 by Induction Baseline Disease Characteristics; UC Maintenance Randomized Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 192 | 376 | | | | | | | | |
| Duration of disease (years) | <2 | 31 | 89 | 204.87 | 216.45 | 4.88 | 2.89 | 14.63 | 2.89 | 34.14 | 47.62 |
| | ≥2 to ≤5 | 62 | 84 | 199.56 | 333.13 | 0.00 | 6.35 | 7.58 | 3.17 | 50.52 | 79.32 |
| | >5 to ≤10 | 49 | 100 | 356.97 | 316.22 | 0.00 | 7.94 | 9.23 | 7.94 | 107.71 | 59.54 |
| | >10 | 50 | 103 | 381.66 | 314.41 | 0.00 | 15.15 | 12.31 | 2.53 | 61.56 | 66.92 |
| Severity of disease | Moderate (modified Mayo score 5-6) | 66 | 139 | 213.92 | 265.98 | 2.18 | 7.57 | 4.37 | 2.84 | 50.20 | 53.95 |
| | Severe (modified Mayo score 7-9) | 126 | 237 | 331.82 | 312.45 | 0.00 | 8.82 | 13.88 | 4.96 | 74.44 | 68.33 |
| Extent of disease | Limited | 96 | 215 | 292.37 | 275.10 | 0.00 | 9.25 | 9.28 | 4.32 | 63.42 | 61.68 |
| | Extensive | 96 | 161 | 284.63 | 321.62 | 1.65 | 7.20 | 11.58 | 4.00 | 67.85 | 64.80 |
| Baseline Mayo endoscopy subscore | Moderate: subscore of 2 | 61 | 130 | 316.69 | 290.70 | 0.00 | 9.05 | 9.82 | 5.03 | 85.92 | 59.35 |
| | Severe: subscore of 3 | 131 | 246 | 275.08 | 297.82 | 1.19 | 7.99 | 10.67 | 3.73 | 55.73 | 65.00 |

19. Note: CNTO1959UCO3001; IS-1 and IS-2; Includes data up to the time of dose adjustment for subjects who had a dose adjustment.
20. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
21. Note: Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.

## Extrinsic factors

*Induction*

**Table 56: Overall Summary of Treatment-emergent Events During Placebo-controlled Induction Period (Week 0 to Week 12) by Concomitant Medications and Medication History; UC Induction Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections[d] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 385 | 629 | | | | | | | | |
| Receiving immunomodulators[a] at induction baseline | Yes | 71 | 144 | 34 (47.9%) | 65 (45.1%) | 4 (5.6%) | 3 (2.1%) | 1 (1.4%) | 1 (0.7%) | 10 (14.1%) | 18 (12.5%) |
| | No | 314 | 485 | 167 (53.2%) | 243 (50.1%) | 22 (7.0%) | 13 (2.7%) | 13 (4.1%) | 7 (1.4%) | 44 (14.0%) | 73 (15.1%) |
| Receiving oral corticosteroids[b] at induction baseline | Yes | 159 | 266 | 82 (51.6%) | 131 (49.2%) | 15 (9.4%) | 6 (2.3%) | 8 (5.0%) | 6 (2.3%) | 22 (13.8%) | 44 (16.5%) |
| | No | 226 | 363 | 119 (52.7%) | 177 (48.8%) | 11 (4.9%) | 10 (2.8%) | 6 (2.7%) | 2 (0.6%) | 32 (14.2%) | 47 (12.9%) |
| ADT failure[c] status at Week 0 | Yes | 187 | 305 | 113 (60.4%) | 164 (53.8%) | 16 (8.6%) | 12 (3.9%) | 8 (4.3%) | 7 (2.3%) | 27 (14.4%) | 46 (15.1%) |
| | No | 198 | 324 | 88 (44.4%) | 144 (44.4%) | 10 (5.1%) | 4 (1.2%) | 6 (3.0%) | 1 (0.3%) | 27 (13.6%) | 45 (13.9%) |
| Without ADT failure[c] at Week 0 | ADT-naïve | 188 | 305 | 83 (44.1%) | 139 (45.6%) | 9 (4.8%) | 4 (1.3%) | 5 (2.7%) | 1 (0.3%) | 26 (13.8%) | 44 (14.4%) |
| | ADT-experienced, without documented failure | 10 | 19 | 5 (50.0%) | 5 (26.3%) | 1 (10.0%) | 0 | 1 (10.0%) | 0 | 1 (10.0%) | 1 (5.3%) |

22. [a] Immunomodulators 6-MP, AZA, or MTX.
23. [b] Includes budesonide and beclomethasone dipropionate.
24. [c] ADT failure is defined as an initial inadequate response, loss of response, or intolerance to TNF antagonists, vedolizumab, or tofacitinib.
25. [d] Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.
26. Note: CNTO1959UCO3001; IS-1 and IS-2.
27. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.

*Maintenance*

**Table 57: Overall Summary of Treatment-emergent Events per Hundred Subject-years of Follow-up During the Maintenance Study Through Week M 44 by Concomitant Medications and Medication History; UC Maintenance Randomized Safety Analysis Set**

| | | N | | TEAE | | Serious TEAE | | TEAE Leading to Discontinuation of Study Agent | | Treatment-Emergent Infections[d] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab | Placebo | Guselkumab |
| Total number of subjects | | 385 | 629 | | | | | | | | |
| Receiving immunomodulators[a] at induction baseline | Yes | 43 | 83 | 255.79 | 253.95 | 3.50 | 5.98 | 17.52 | 0.00 | 49.06 | 59.75 |
| | No | 149 | 293 | 298.34 | 307.94 | 0.00 | 9.08 | 8.29 | 5.45 | 70.44 | 64.04 |
| Receiving oral corticosteroids[b] at induction baseline | Yes | 79 | 148 | 324.87 | 263.08 | 0.00 | 6.46 | 14.39 | 2.77 | 74.02 | 65.54 |
| | No | 113 | 228 | 265.57 | 314.90 | 1.31 | 9.51 | 7.85 | 5.03 | 60.18 | 61.53 |
| ADT failure[c] status at Week 0 | Yes | 76 | 164 | 426.63 | 371.91 | 0.00 | 10.82 | 16.50 | 5.82 | 77.78 | 76.54 |
| | No | 116 | 212 | 217.79 | 240.23 | 1.21 | 6.59 | 7.26 | 3.00 | 59.29 | 53.32 |
| Without ADT failure[c] at Week 0 | ADT-naïve | 109 | 200 | 218.90 | 245.90 | 1.30 | 6.35 | 7.77 | 2.54 | 62.17 | 54.01 |
| | ADT-experienced, without documented failure | 7 | 12 | 202.10 | 146.69 | 0.00 | 10.48 | 0.00 | 10.48 | 18.37 | 41.91 |

28. [a] Immunomodulators 6-MP, AZA, or MTX.
29. [b] Includes budesonide and beclomethasone dipropionate.
30. [c] ADT failure is defined as an initial inadequate response, loss of response, or intolerance to TNF antagonists, vedolizumab, or tofacitinib.
31. [d] Infections were defined as any AEs which were coded to the MedDRA SOC 'Infections and infestations'.
32. Note: CNTO1959UCO3001; IS-1 and IS-2; Includes data up to the time of dose adjustment for subjects who had a dose adjustment.
33. Note: Includes only subjects with modified Mayo score 5-9 at induction baseline who were randomized in the Maintenance Study.

### *2.6.8.7. Immunological events*

The effect of immunogenicity on safety is presented in Section 2.6.2. Clinical pharmacology.

### *2.6.8.8. Safety related to drug-drug interactions and other interactions*

There are no updates on drug-drug interactions with guselkumab.

In the VEGA study investigating guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis, at week 50, 45 (63%) of 71 patients in the combination therapy group, 55 (76%) of 72 patients in the golimumab monotherapy group, and 46 (65%) of 71 patients in the guselkumab monotherapy group had reported at least one adverse event. The most common adverse events were ulcerative colitis, upper respiratory tract infection, headache, anaemia, nasopharyngitis, neutropenia, and pyrexia. No deaths, malignancies, or cases of tuberculosis were reported during the combination induction period. During the monotherapy phase, one case of tuberculosis of intrathoratic lymph nodes and pulmonary embolism were reported in the same patient

in the combination therapy→ guselkumab monotherapy group. Two deaths were reported after the final dose of study intervention (poisoning in the combination therapy group and COVID-19 in the guselkumab monotherapy group).

### *2.6.8.9. Discontinuation due to adverse events*

Across the QUASAR programme, most discontinuations were due to AEs associated with the underlying disease of UC.

*Placebo-controlled Induction - QUASAR IS-1 and IS-2 Pooled*

The proportions of participants with 1 or more AEs leading to discontinuation of study intervention were low across the pooled QUASAR IS-1 and IS-2 treatment groups were as follows:

- 1.5% of participants in the guselkumab 200 mg IV group.
- No participants in the guselkumab 400 mg IV group.
- 3.6% of participants in the placebo IV group.

The most common AE leading to discontinuation of study intervention was colitis ulcerative.

*Maintenance*

The proportions of participants with 1 or more AEs leading to discontinuation of study intervention through Week M-44 were were as follows:

- 2.6% participants in the guselkumab 200 mg SC q4w group.
- 3.8% participants in the guselkumab 100 mg SC q8w group.
- 6.8% participants in the placebo SC group.

The most common AE leading to discontinuation of study intervention was UC.

### *2.6.8.10. 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 enrolment 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.

During the procedure, the MAH provided a review of the postmarketing cases related to MACE:

Cumulatively through 12 July 2024 (cutoff date for the latest PBRER), 587 postmarketing cases reporting events related to MACE were identified. The most frequently reported indications in these cases were psoriasis and PsA (>99.3% of reports). The cases with sufficient information for a meaningful medical assessment were reported in patients receiving multiple medications and occurred in the context of prior history of stroke or MI, or other pre-existing cardiovascular comorbidities and conditions known to represent independent factors increasing the risk for adverse cardiovascular or cerebrovascular events.

Considering the estimated cumulative exposure of 588,988 person-years, the estimated cumulative reporting rate is 0.1 per 100 person-years. This reporting rate (1 per 1,000 person-years) is consistent with published data showing that the incidence of MACE among patients with severe psoriasis ranged from 3.1 to 16.2 per 1,000 person-years compared with control populations which ranged from 2.0 to 10.6 per 1,000 person-years. Crude incidence rates of composite cardiovascular disease ranged from 7.3 to 15.9 per 1,000 person-years among psoriasis patients treated with biologics and 8.3 to 16.7 per 1,000 person-years among psoriasis patients treated with non-biologics; after multivariable adjustment there was no significant difference between any of the psoriasis treatments.

**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.

## 2.6.9. Discussion on clinical safety

The key safety data to support the safety of guselkumab IV induction and guselkumab SC maintenance treatment in adult patients with moderately to severely active UC are from the CNTO1959UCO3001 (QUASAR) programme including 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter studies conducted under a single protocol. Supportive safety data were provided from a Phase 2a study in UC (CNTO1959UCO2002; VEGA study), Phase 2 and Phase 3 studies in CD (CNTO1959CRD3001; [GALAXI 1, GALAXI 2, and GALAXI 3] and CNTO1959CRD3004 [GRAVITI]), and Phase 2 and Phase 3 studies in the approved indications of plaque psoriasis and PsA.

The safety database is considered sufficient to characterise the safety profile in the UC indication. Upon the CHMP's request, the MAH provided long-term safety data through 31 January 2024 in the

QUASAR Maintenance Study. However, it is noted that no formal database lock was performed for this Safety Update Report, and data collected after Week M-44 through 31 January 2024 in the QUASAR Maintenance Study have not been thoroughly cleaned and finalised.

**Overall safety**

In the QUASAR induction studies, frequencies of the safety events (AEs, SAEs, AEs leading to discontinuation) were rather similar in the different treatment groups. No dose dependency was observed. In QUASAR Maintenance study, frequency of AEs and SAEs are slightly higher in the 200 mg sc. Q4W treatment group than in the 100 mg sc. Q8W group.

In studies IS-1 and IS-2, no special trend of AE frequency can be drawn for the majority of SOCs. No PT was reported in more than 2 participants in the combined guselkumab group except for ulcerative colitis (n=7) and anaemia (n=3).

In the Skin and subcutaneous system disorders SOC, the AE frequency is led by the Pruritus events in the Guselkumab 200 mg treatment group. Frequency of the rash AE, a known ADR of guselkumab, as well as frequency of pruritus AE showed some dose dependency in the QUASAR maintenance study. Upon the CHMP's request, the MAH provided the liver function test results for patients experiencing pruritus AE. Among them, there was one patient who had mild liver enzyme elevations with temporal association with pruritus event. No product information update is deemed necessary with regards pruritus. The frequency of the ADR rash in the SmPC Section 4.8 is updated from uncommon to common.

A trend for dose-dependency of the frequency for the AE arthralgia was seen in study IS-1, but no such trend was observed in the study IS-2. It is acknowledged that peripheral arthritis is a well-known extraintestinal manifestation of UC and the arthralgia might be a sign of it. However, if the IL-23 had a role in the arthritis in UC patients, the opposite trend (i.e. decrease of the incidence of arthralgia AE) would be foreseen during the guselkumab treatment. Recent literature data (Lee et al, 2022[41]) also suggest the direct role of IL-23 in the pain regulation in arthritis. Hence, no product information update is deemed necessary.

Hypertension AE occurred with a higher frequency in the 400 mg guselkumab group than in the 200 mg group in study IS-1. In both studies IS-1 and IS-2, the frequency of AEs in the Vascular disorder SOC were led by the Hypertension PT even with low patient number and frequencies. Albeit hypertension is a known comorbidity of UC, the CHMP asked for further clarifications since hypertension has not been identified as an adverse reaction of the guselkumab in PsO and PsA studies. Upon the CHMP's request, the MAH provided the results of blood pressure observations at study visits as well as their changes from baseline values. During the induction period, the maximum systolic BP was 179 mmHg, 52 mmHg of maximum elevation of systolic BP from the baseline was observed. As for diastolic BP, maximum diastolic BP of 114 mmHg and maximum elevation from the baseline of 43 mmHg were observed. In the randomised population during the maintenance period, the maximum systolic BP was 180 mmHg, and 58 mmHg of maximum elevation of systolic BP from the baseline was observed. As for diastolic BP, maximum diastolic BP of 115 mmHg and maximum elevation from the BL of 46 mmHg were observed. Considering that the mean and median systolic and diastolic BP values seem to be well within the normal BP range, as well as their mean and median changes close to 0 during the induction and maintenance parts of the QUASAR programme, the issue was not further pursued.

One case of pregnancy was reported, in Study IS-2, the patient was likely not exposed to gueslkumab.

[41] Lee, Kevin M-C., Jonathan P. Sherlock, and John A. Hamilton. "The role of interleukin (IL)-23 in regulating pain in arthritis." *Arthritis research & therapy* 24.1 (2022): 89.

In the maintenance study, the lowest AE frequency was observed in the sc. 100 mg guselkumab Q8W group for the majority of SOCs and PTs compared to the Placebo group and the 200 mg Q4W guselkumab group. Nevertheless, a dose-dependency was observed for the pyrexia PT, which is not a known ADR for guselkumab. Upon the CHMP's request, the MAH provided a thorough assessment of pyrexia events. Most of them were found to be in temporal association with COVID or other infections, flare of the UC or with the administration of a COVID-vaccine. Two Pyrexia events remained without plausible explanation. Taking into account all the above and also the lack of a possible mechanism of development of pyrexia by guselkumab, pyrexia events can be considered as not related to the administration of the guselkumab most likely.

**Death**

There were no deaths reported in QUASAR IS-1.

In QUASAR IS-2, 3 deaths were reported. One death case in the guselkumab 200 mg iv. group was a fatal acute myocardial infarction in a participant with pre-existing cardiovascular risk factors. Two cases occurred in the placebo group (reported terms: natural causes and cardiac arrest). Medical history of the participant reported as death due to natural causes included pre-existing cardiovascular risk factors, whereas the other placebo patient was obese, but the patient did not have other CV risk factors.

In the QUASAR-M, no death occurred through Week M-44.

**Serious AEs**

In the induction studies, the proportion of participants with 1 or more SAEs was numerically higher in the placebo group compared with the guselkumab groups. The proportion of participants with SAEs was the lowest in the Placebo group (0.5%) and the highest in the guselkumab 200 mg SC q4w group (6.3%) for the UC Maintenance Randomized Safety Analysis Set (n=192). However, the MAH pointed out that a lower number of SAEs was reported in the placebo group than could be expected from earlier UC studies with similar study designs and safety collection methodologies as well as in external similarly designed UC maintenance studies. The MAH's explanation on the SAE frequencies in Placebo group in the UC Maintenance Randomized Safety Analysis Set is acceptable to the CHMP.

The SAEs reported in the guselkumab 200 mg group did not have a pattern with respect to individual PTs or SOCs and the majority of these SAEs were assessed as unrelated to study intervention by the investigator. Through Week M-44, UC (n=2) and anxiety (n=2) were the only SAEs reported in more than one guselkumab-treated participant. A number of the reported PTs lacked biological plausibility for a causal relationship given the mechanism of action of guselkumab.

**AESIs-Malignancies**

One patient experienced adenocarcinoma of the rectum during the Maintenance study. While the relationship of this event with the guselkumab treatment cannot be fully excluded, the CHMP noted that this patient with a long-standing and extended UC could be considered predisposed to colon/rectal carcinoma .

Basal cell carcinoma and squamous cell carcinoma AEs were reported in 3 patients treated with guselkumab, these events were considered by the MAH as possibly not related. This is agreed by the CHMP since 2 of these patients had the same type of non-melanoma skin cancer in the medical history; for the 3$^{rd}$ patient, the pre-existence of the skin spot diagnosed later on as basal cell carcinoma, was documented before the initiation of the study.

One participant in the non-randomized guselkumab 200 mg SC q4w group had clear cell renal cell carcinoma which was considered not related to the study treatment. This is agreed by the CHMP.

Three participants had breast cancer, two of the cases were reported in patients treated with guselkumab in the induction phase, the third case was reported in a patient who received guselkumab during the induction phase, however, the event is not considered related to the study drug.

**Other Significant AEs**

Frequencies of infections in the pooled IS-1 and IS 2 studies were reported at similar frequencies in the Placebo and 200 mg Guselkumb group, whereas a lower AE frequency was observed in the 400 mg Guselkumab group. This trend seen in other SOCs than infections were observed in previous UC clinical studies (Rutgeerts 2005[42]; Sandborn 2014[43]; Sands 2019[44] for Applicant's previous UC studies, Danese 2022[45]; D'Haens 2023[46] for contemporary external UC maintenance studies).

In the maintenance study, very similar infection AE frequencies were found in the Placebo and the two Guselkumab maintenance dose groups. The CHMP noted the high frequencies, close to 30%, but the majority of them were COVID-19. Most infections were non-serious, mild or moderate in intensity, and did not result in discontinuation of study intervention. The CHMP considers that infections reported in UC do not raise new specific concern on guselkumab safety.

There were 3 fatal MACE events, none of these cases were considered related to the study treatment. However, the CHMP noted that the MAH's assignment of one case as MACE in a patient treated with placebo is not agreed since no autopsy was carried out. Hence, the exact cause of the death remains unknown.

Throughout the QUASAR programme, all guselkumab-treated participants with VTE had a medical history of prior VTE. An increased risk of VTE in patients with IBD compared with the general population is well documented (Magro 2014[47]; Souto 1995[48]; Weng 2018[49]; Yoshida 2009[50]). The CHMP concluded that the data available do not suggest an increased risk of thrombotic events with guselkumab treatment.

Throughout the QUASAR programme, no clinically important hepatic disorders and no events meeting the biochemical criteria for Hy's law were reported. The proportions of participants with hepatic disorder AEs were similar across the treatment groups.

In the induction studies, the most commonly reported PTs in the Investigations SOC were alanine aminotransferase increased, aspartate aminotransferase increased, and gamma glutamyltransferase increased. Some trends of increased AE frequencies with increasing guselkumab exposure was seen. In the Maintenance study, the most commonly reported PTs in the Investigations SOC were gamma-glutamyltransferase increased, alanine aminotransferase increased, and blood bilirubin increased. Liver enzyme-related AE frequency was the highest in the 100 mg Q8W Guselkumab dose group (3.8%), however, this was considered as a chance finding.

[42] Paul Rutgeerts et al. "Infliximab for Induction and MaintenanceTherapy for Ulcerative Colitis" *N Engl J Med 2005;353:2462-76.*
[43] William J. Sandborn et al. "Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-to-Severe Ulcerative Colitis" *Gastroenterology 2014;146:96–109*
[44] B.E. Sands et al. "Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis" *N Engl J Med 2019;381:1201-14.*
[45] Silvio Danese et al. "Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials." *Lancet 2022; 399: 2113–28*
[46] Geert D'Haens et al. "Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis" *N Engl J Med 2023;388:2444-55.*
[47] Magro, Fernando, João-Bruno Soares, and Dália Fernandes. "Venous thrombosis and prothrombotic factors in inflammatory bowel disease." *World journal of gastroenterology: WJG* 20.17 (2014): 4857.
[48] Souto, Joan Carles, et al. "Prothrombotic state and signs of endothelial lesion in plasma of patients with inflammatory bowel disease." *Digestive diseases and sciences* 40 (1995): 1883-1889.
[49] Weng, Meng-Tzu, et al. "Incidence and risk factor analysis of thromboembolic events in East Asian patients with inflammatory bowel disease, a multinational collaborative study." *Inflammatory bowel diseases* 24.8 (2018): 1791-1800.
[50] Yoshida, Hideo, and Neil D. Granger. "Inflammatory bowel disease: a paradigm for the link between coagulation and inflammation." *Inflammatory bowel diseases* 15.8 (2009): 1245-1255.

Throughout the QUASAR programme, the proportions of participants with suicidal ideation, suicidal behaviour, or self-injurious behaviour were similar across the treatment groups. There were no completed suicide events.

No concern was raised following the review of the AEs leading to discontinuation.

**Safety in different subgroups**

The majority of the patients included in the QUASAR programme were below 65 years of age, there were only few patients in the 65-74 and 75-84 year age groups; and no patient above 85 years. A comparison of elderly and non-elderly (below 65 years) age groups showed a trend for higher frequencies of TEAEs, SAEs and infections in the Guselkumab groups in the elderly. The available data do not suggest specific concerns of guselkumab in the elderly. However, the CHMP acknowledged that the safety data available in the elderly are limited and that no firm conclusion can be drawn at the moment. The use in patients ≥ 65 years is listed as missing information in the RMP.

Analyses per other baseline demography characteristics in the guselkumab induction group did not suggest specific concerns in the subgroups. In the Maintenance study, higher adverse event rates were observed in the elderly subpopulation, in female patients and in patients above 70 kg. However, considering the low number of patients in the subgroups other than White and/or Hispanic, no firm conclusion can be drawn .

Analyses per baseline disease characteristics do not suggest an impact on the safety of guselkumab induction in UC. For most parameters, AE frequencies are similar or slightly lower in the guselkumab treatment group (UC Induction safety Analysis Set). There were two exemptions, both in the Disease duration of ≥2 to ≤5 subpopulation, where TEAE and Infection AE frequencies were slightly higher in the guselkumab group. In the Maintenance study, AEs rates were generally higher in patient subgroups of higher disease burden for both placebo and guselkumab groups. The available data do not suggest specific concerns of the safety of guselkumab in more severe disease.

As for extrinsic factors, the analyses per baseline UC therapy indicate similar AE frequencies in the Placebo and the Guselkumab groups for all baseline UC therapy subgroups. In the baseline oral CS subgroup, the SAE frequency was higher in the placebo group compared to the CS-free subpopulation. In the guselkumab groups of both CS – related subpopulation, the SAE frequencies were similar to each other. The ADT-status had a clear impact on AE frequencies in the induction studies, as remarkably higher frequencies were observed in the ADT-failed group. Taking into consideration that AE frequencies of ADT-failed guselkumab patient group were definitely lower than the ADT-failed Placebo patients, the below finding might be the consequence of the more severe UC status of the ADT-failed subgroup rather than a negative safety effect. Similar observation was found in the maintenance study, as ADT failed patients had much higher adverse event rates compared to the ADT non-failed ones (most of whom were ADT naive).

**Laboratory data**

More patients experienced neutrophil count decrease in the guselkumab treatment groups than the placebo group, the majority of these events were of Grade 1 severity, in the IS-1 and the IS-2 studies. Neutrophil count decrease is a known adverse reaction of guselkumab (frequency uncommon), hence no product information update is needed.

Decreased haemoglobin levels were common in the QUASAR studies and shift of the haemoglobin level towards a more severe grade was observed regardless the study treatment. Deteriorating effect of UC on the iron absorption resulting in low haemoglobin level and iron deficiency anaemia are well-known complications of the UC condition. Hence, the relationship between the haemoglobin decrease and the guselkumab treatment is very unlikely.

The majority of subjects had normal liver function (ALT, AST, AP and total bilirubin) at baseline. Most of them did not experience liver function elevations during the induction studies. The majority of the liver function elevations was in the 1xULN-3xULN range with no clear differences between the treatment groups of the UC induction safety analysis set. In the maintenance study, liver function elevation frequencies and severities were similar to those observed in UC induction phase. Transaminase increased are listed as common ADR in the SmPC Section 4.8, therefore, no product information update is needed.

**Long-term safety data**

Upon the CHMP's request, the MAH provided additional safety data available after Week M-44 through 31 January 2024 for the QUASAR Maintenance Study.

In the Safety Update Reporting Period of QUASAR programme, there were 2 cases of MACE (1 acute coronary syndrome and 1 thrombotic cerebral infarction) in 2 guselkumab-treated participants and 2 cases of MACE in 2 participants treated with placebo. The occurrence of MACE events was raised as a potential concern. The MAH clarified that the guselkumab-treated participants had pre-existing risk factors (history of angina, MI, VTE among others) for the MACE events. Further, there is an elevated risk of atherosclerosis, MI, stroke and CV death in IBD patients and a lack of biologically plausible mechanism through which the inhibition of IL-23 might affect MACE and CV events' risk. Reviews of MACE and CV events other than MACE accross the indications (UC, CD, PSO and PSA) did not raise new concerns. Postmarketing experience in PSO and PSA patients shows that MACE events occurred in patients with multiple medications and prior history of stroke, MI or other CV comorbidities as well as conditions known to represent independent factors increasing the risk for adverse cardiovascular or cerebrovascular events. MACE is listed as an important potential risk for guselkumab, monitoring via routine and additional PV activities remains sufficient to address this potential risk.

The safety profiles of both the guselkumab 100 mg SC q8w and 200 mg SC q4w and dose regimens remain unchanged with those reported in the initial UC application and are comparable to the safety profile of guselkumab in the approved indications of plaque psoriasis and PsA.

VEGA study was a Phase 2 study, including 214 UC patients as Safety Analysis set randomised in 1:1:1 ratio to golimumab, guselkumab or combination therapy. Overall, the safety characteristics and the frequencies of treatment emergent AEs were rather similar for the golimumab, guselkumab and the combination groups. The SAEs of pulmonary embolism and tuberculosis of intrathoracic lymph nodes in the combination group are of serious concern. Due to the low patient numbers in this study, it is hard to draw conclusions on the combination of guselkumab with golimumab. Further, a metaanalysis data for Rheumatoid Arthitis patients suggest negative effect of the combination of guselkumab and golimumab on the safety in RA. (Hirten et al, 2018[51]). The MAH did not propose the above-mentioned combination in the SmPC, and this is agreed by the CHMP.

Safety results from the postmarketing safety data sources did not indicate new safety concern for guselkumab. Section 4.6 of the SmPC is updated to indicate that there is limited data from the use of guselkumab in pregnant women.

Overall, no new safety concern was identified from the data available in patients with CD. Following updated pooled safety analysis derived from psoriasis, PsA, UC, and CD clinical studies and postmarketing experience, the frequency of the following adverse reaction is updated in SmPC Section 4.8:

- Rash: from uncommon to common

[51] Hirten, Robert P., et al. "Combining biologics in inflammatory bowel disease and other immune mediated inflammatory disorders." *Clinical Gastroenterology and Hepatology* 16.9 (2018): 1374-1384.

## 2.6.10. Conclusions on the clinical safety

Comprehensive safety data from adult participants with moderately to severely active UC treated with guselkumab induction (200 mg IV at Weeks I-0, I-4, and I-8) followed by guselkumab maintenance (200 mg SC q4w or 100 mg SC q8w) thereafter are consistent with the well characterized safety profile of guselkumab in its approved indications of psoriasis and PsA.

# *2.7. Risk Management Plan*

## 2.7.1. 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 |

## 2.7.2. 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<br>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<br>Not applicable | | | | |
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| C0168Z03 (PSOLAR)<br><br>Ongoing | To study the long-term safety of guselkumab | • Serious infection<br>• Malignancy<br>• Serum sickness<br>• Major adverse cardiovascular events (MACE)<br>• Exposure during pregnancy<br>• Use in patients ≥65 years of age<br>• Long-term safety of guselkumab | Protocol submission | March 2018 |
| | | | Registry start | 20 June 2007:<br>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 |

| Study and Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| | | | End of data collection for TREMFYA | 4Q 2029 |
| | | | Final report | 4Q 2030 |
| CNTO1959PSO4001 (PsoBest)<br><br>Ongoing | To study the long-term safety of guselkumab | • Serious infection<br>• Malignancy<br>• Serum sickness<br>• Major adverse cardiovascular events (MACE)<br>• Exposure during pregnancy<br>• Use in patients ≥65 years of age<br>• Long-term safety of guselkumab | Protocol submission | March 2018 |
| | | | Registry start | January 2008:<br>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 |
| PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study)<br><br>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<br><br>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<br>• Malignancy<br>• Serum sickness<br>• Major adverse cardiovascular events (MACE)<br>• 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 |

| Study and Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| Long-term extension of Study CNTO1959UCO3004<br><br>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<br>• Malignancy<br>• Serum sickness<br>• Major adverse cardiovascular events (MACE)<br>• 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 |

## 2.7.3. Risk minimisation measures

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Serious infection | **Routine risk minimization measures:**<br><br>SmPC Section 4.3 (Contraindications)<br><br>SmPC Section 4.4 (Special Warnings and Precautions for Use)<br><br>Package Leaflet Section 2 (What you need to know before you use Tremfya)<br><br>PL Section 4 (Possible side effects)<br><br>**Additional risk minimization measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>TOI TFUQ<br><br>**Additional pharmacovigilance activities:**<br><br>C0168Z03 (PSOLAR)<br><br>Final report: 4Q 2030<br><br>CNTO1959PSO4001 (PsoBest)<br><br>Final report: 4Q 2030<br><br>Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001<br><br>Final report: 3Q 2028<br><br>Long-term extension of Study CNTO1959UCO3004<br><br>Final report: 4Q 2029 |
| Malignancy | **Routine risk minimization measures:**<br><br>None<br><br>**Additional risk minimization measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>TOI TFUQ<br><br>**Additional pharmacovigilance activities:**<br><br>C0168Z03 (PSOLAR)<br><br>Final report: 4Q 2030 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | | CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030<br>Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001<br>Final report: 3Q 2028<br>Long-term extension of Study CNTO1959UCO3004<br>Final report: 4Q 2029 |
| Serum sickness | **Routine risk minimization measures:**<br>SmPC Section 4.3 (Contraindications)<br>SmPC Section 4.4 (Special Warnings and Precautions for Use)<br>Package Leaflet Section 2 (What you need to know before you use Tremfya)<br>PL Section 4 (Possible side effects)<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOIQ<br>**Additional pharmacovigilance activities:**<br>C0168Z03 (PSOLAR)<br>Final report: 4Q 2030<br>CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030<br>Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001<br>Final report: 3Q 2028<br>Long-term extension of Study CNTO1959UCO3004<br>Final report: 4Q 2029 |
| Major adverse cardiovascular events (MACE) | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>TOI TFUQ<br>**Additional pharmacovigilance activities:**<br>C0168Z03 (PSOLAR)<br>Final report: 4Q 2030<br>CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030<br>Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001<br>Final report: 3Q 2028<br>Long-term extension of Study CNTO1959UCO3004<br>Final report: 4Q 2029 |
| Exposure during pregnancy | **Routine risk minimization measures:**<br>SmPC Section 4.6 (Fertility, | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Follow-up of reported pregnancies |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | Pregnancy and Lactation)<br>Package Leaflet Section 2 (What you need to know before you use Tremfya)<br>**Additional risk minimization measures:**<br>None | **Additional pharmacovigilance activities:**<br>C0168Z03 (PSOLAR)<br>Final report: 4Q 2030<br>CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030<br>PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study)<br>Final report: 2Q 2031 |
| Use in patients ≥65 years of age | **Routine risk minimization measures:**<br>SmPC Section 4.2 (Posology and Method of Administration)<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>C0168Z03 (PSOLAR)<br>Final report: 4Q 2030<br>CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030 |
| Long-term safety of guselkumab | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None.<br>**Additional pharmacovigilance activities:**<br>C0168Z03 (PSOLAR)<br>Final report: 4Q 2030<br>CNTO1959PSO4001 (PsoBest)<br>Final report: 4Q 2030<br>Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001<br>Final report: 3Q 2028<br>Long-term extension of Study CNTO1959UCO3004<br>Final report: 4Q 2029 |

### 2.7.4. Conclusion

The CHMP considered that the risk management plan version 10.4 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

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

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.9. Product information*

### 2.9.1. User consultation

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

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

UC is an inflammatory bowel disorder of unknown aetiology characterized by chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors (Ordás 2012[52]; Danese 2004[53]; Podolsky 2002[54]; Stenson 2000[55]). UC is most commonly diagnosed in late adolescence and early adulthood, but UC may present at any age (Loftus 2004[56]). Clinically, patients with UC suffer from diarrhoea, rectal bleeding, weight loss, abdominal pain, bowel urgency, fatigue, fever, and may also display prominent extraintestinal manifestations, most commonly arthritis (Regueiro 2023[57]; Ordás 2012[58]; Stenson 2000[59]; Caron 2023[60]; Dubinsky 2022[61]). UC is characterized by a life-long relapsing and remitting course, with 15% of patients having an acute exacerbation requiring hospitalization at some time during their illness (Willert 2008[62]). In severe UC, the bowel wall may become extremely thin, the mucosa denuded, and the inflammation may extend to

[52] Ordás I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619.
[53] Danese S (2019), Allez M, van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Dig Dis. 2019;37(4):266-283.
[54] Podolsky DK (2002). Inflammatory bowel disease. N Engl J Med. 2002;347(6):417-429.
[55] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[56] Loftus EV Jr (2004). Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-1517.
[57] Regueiro M (2023), Hunter T, Lukanova R, et al. Burden of fatigue among patients with ulcerative colitis and Crohn's disease: results from a global survey of patients and gastroenterologists. Adv Ther. 2023;40(2):474-488.
[58] Ordás I (2012), Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-1619.
[59] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[60] Caron B (2023), Ghosh S, Danese S, Peyrin-Biroulet L. Identifying, Understanding, and Managing Fecal Urgency in Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2023;21(6):1403-1413.
[61] Dubinsky MC (2022), Panaccione R, Lewis JD, et al. Impact of Bowel Urgency on Quality of Life and Clinical Outcomes in Patients With Ulcerative Colitis. Crohns Colitis 360. 2022;4(3):otac016.
[62] Willert RP (2008), Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependant and refractory ulcerative colitis. World J Gastroenterol. 2008;14(16):2544-2549.

the serosa leading to dilatation, toxic megacolon, and subsequent perforation (Glickman 1998[63]; Stenson 2000[64]). Within 10 years of diagnosis, approximately 20% of adults with UC are reported to have undergone colectomy (Van Limbergen 2008[65]).

A systematic review of studies evaluating the worldwide incidence and prevalence of inflammatory bowel disease reported that the prevalence rates for UC were 2.4 to 505 per 100,000 persons in Europe (Ng et al. 2017[66]).

### 3.1.2. Available therapies and unmet medical need

Conventional therapies for the treatment of UC include 5-ASA–containing medications, corticosteroids, and immunomodulators such as AZA and 6-MP (Kobayashi 2020[67]). Treatment with 5-ASA therapy has been shown to be efficacious and safe as monotherapy for induction of moderately but not severely active UC. Corticosteroids are effective for the induction of remission but are not an option for maintenance therapy due to cumulative toxicity and lack of long-term efficacy. Thiopurines are slow acting and monotherapy with thiopurines does not induce remission in moderately to severely active UC. Treatment with advanced therapies with biologics or small molecules may be considered if corticosteroids or immunomodulators fail to achieve or maintain remission (Revés 2021[68]; Côté Daigneault 2015[69]). However, clinical guidance supports early use of biologics rather than gradual step-up therapy in patients with moderate to severe disease activity at increased risk for colectomy (Feuerstein 2020[70]). Delaying effective treatment to induce remission may be harmful and increase the risk of UC-related complications, hospitalization, colectomy, and inferior quality of life in patients with predictors of colectomy such as extensive UC disease, severe endoscopic activity, early need for corticosteroids, and elevated inflammatory markers (Yarur 2011[71]; Burisch 2017[72]).

Approved biologic therapies for the treatment of UC include anti-TNFα agents, an α4β7 integrin antagonist, an anti-IL-12/23 antibody and an anti-IL-23 antibody mirikizumab. Small molecule advanced therapies include JAK inhibitors and S1P receptor modulators. Approximately one third of patients do not respond initially to advanced therapies, and an additional 10% of responders lose their initial response over the course of treatment, resulting in treatment switch or dose adjustment (Afzali 2023[73]; Privitera 2021[74]; Danese 2019[75]; Sands 2019[76]). Furthermore, there are associated safety

[63] Glickman RM (1998). Inflammatory bowel disease: ulcerative colitis and Crohn's disease. In: Faluce AS, Braunwald E, eds. Harrison's Principles of Internal Medicine, 14th ed. New York, NY: McGraw-Hill;1998;1633 1645.
[64] Stenson WF (2000). Inflammatory bowel disease. In: Goldman l, Bennett, JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders Co; 2000;722-729.
[65] Van Limbergen J (2008), Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135(4):1114-1122.
[66] Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., ... & Kaplan, G. G. (2017). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet*, *390*(10114), 2769-2778.
[67] Kobayashi T (2020), Siegmund B, Le Berre C, et al. Ulcerative colitis. Nat Rev Dis Primers. 2020;6(1):74.
[68] Revés J (2021), Ungaro RC, Torres J. Unmet needs in inflammatory bowel disease. Curr Res Pharmacol Drug Discov. 2021;2:100070.
[69] Côté-Daigneault J (2015), Bouin M, Lahaie R, Colombel J-F, Poitras P. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterology Journal. 2015;3(5):419-428.
[70] Feuerstein JD (2020), Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020;158(5):1450-1461.
[71] Yarur AJ (2011), Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2011;7(10):652-659.
[72] Burisch J (2017), Ungaro R, Vind I, et al. Proximal disease extension in patients with limited ulcerative colitis: a danish population-based inception cohort. Journal of Crohn's and Colitis. 2017;11(10):1200-1204.
[73] Afzali A (2023), Lukanova R, Hennessy F, et al. Unmet Needs in Real-World Advanced Therapy-Naïve and -Experienced Patients with Moderately to Severely Active Ulcerative Colitis in the United States. Adv Ther. 2023;40(4321–4338).
[74] Privitera G (2021), Pugliese D, Rapaccini GL, Gasbarrini A, Armuzzi A, Guidi L. Predictors and Early Markers of Response to Biological Therapies in Inflammatory Bowel Diseases. J Clin Med. 2021;10(4):853.
[75] Danese S (2019), Allez M, van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Dig Dis. 2019;37(4):266-283.
[76] Sands BE (2019), Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-1214.

risks with some currently approved advanced therapies, including warnings related to serious infections, mortality, malignancy, major adverse cardiovascular events, or thrombosis.

Surgery may be pursued in severe refractory UC. Surgery involves complete removal of potential disease-bearing tissue and may require removing the entire colon and rectum. Surgery is associated with reduced quality of life and risk of complications including pouchitis, stricture, pelvic sepsis, faecal incontinence, sexual dysfunction, and female infertility (Matsuoka 2023[77]; Guaraldi 2018[78]; Ramos-Andrade 2016[79]; Hahnloser 2007[80]).

In summary, there is an unmet medical need for additional efficacious therapeutic options in UC and a favourable safety profile for patients with an inadequate response to or intolerance to conventional and/or advanced therapies, especially over the long term.

### 3.1.3. Main clinical studies

The efficacy for guselkumab in UC is based on data from 2 Phase 3 studies (Induction Study 2 (IS-2) and Maintenance Study (M)) and supported by a Phase 2b induction dose-ranging study (Induction Study 1; IS-1) conducted under a single protocol, CNTO1959UCO3001 (QUASAR). All 3 QUASAR studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies that evaluated the efficacy and safety of guselkumab in adults with moderately to severely active UC with a history of an inadequate response or failure to tolerate conventional (ie, 6-MP, AZA, or corticosteroids) or ADT (ie, TNF antagonists, vedolizumab, or tofacitinib). These studies provide 56 weeks (12 weeks of IV induction + 44 weeks of SC maintenance) of guselkumab treatment experience. Long-term extension of the QUASAR-M study is ongoing.

## *3.2. Favourable effects*

Statistically significant therapeutic responses were achieved on the primary and most of the major secondary efficacy endpoints of clinical response and remission, symptomatic remission, endoscopic healing and histologic-endoscopic mucosal healing both in induction and maintenance settings. Guselkumab treatment provided also early and clinically relevant effect on individual symptoms such as stool frequency and rectal bleeding, endoscopic outcomes, PD biomarkers CRP and faecal calprotectin and a set of PROs in the induction setting and maintenance of these therapeutic effects was observed in the maintenance setting. Corticosteroid-sparing effect has also been observed during the maintenance study.

The PROs of PROMIS-fatigue response and IBDQ remission were type I error-controlled key secondary endpoints with statistically significant and clinically relevant outcomes during the QUASAR program, hence results on these PROS are included in the SmPC Section 5.1.

Efficacy was shown for all subgroups according to ADT status (naïve, nonfailure or failure), a lower efficacy was nevertheless observed in the ADT-failure subgroup.

[77] Matsuoka K (2023), Yamazaki H, Nagahori M, et al. Association of ulcerative colitis symptom severity and proctocolectomy with multidimensional patient-reported outcomes: a cross-sectional study. J Gastroenterol. 2023;58(8):751-765.
[78] Guaraldi G (2018), Malagoli A, Calcagno A, et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65 - 74 years and more than 75 years. BMC Geriatr. 2018;18(1):99.
[79] Ramos-Andrade D (2016), Andrade L, Ruivo C, Portilha MA, Caseiro-Alves F, Curvo-Semedo L. Imaging the postoperative patient: long-term complications of gastrointestinal surgery. Insights Imaging. 2016;7(1):7-20.
[80] Hahnloser D (2007), Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg. 2007;94(3):333-340.

For non-responders patients to the three iv. induction doses who received three additional sc. doses of 200 mg guselkumab, increases in primary and key secondary outcomes were seen at Week M-44, compared to the key outcomes at Week I-24. This supports the recommendation to consider a maintenance dose of 200 mg for patients who do not show adequate therapeutic benefit to induction treatment.

The initially applied indication was not fully consistent with the patient population included in the QUASAR programme. In the ADT-failed population of QUASAR study, almost 90% failed at least one TNF-alfa inhibitor, approximately half failed vedolizumab and about 20.0% failed tofacitinib. The CHMP agreed that results from failure to tofacitinib could be extrapolated to other medicinal products within the JAK inhibitor therapeutic class. Furthermore, the CHMP noted that the subgroup analyses in patients who failed JAKis are limited to tofacitinib only in a few patients. Considering that conventional treatment or a biologic treatment includes the JAK inhibitors, upon the CHMP's request, the MAH agreed to remove *patients with inadequate or lost reponse or failure JAK inhibitors* in the wording of the indication. Further, only few patients were in the "intolerance" subcategory. However, in line with the other biologics authorised in the UC indication, the CHMP agreed with an indication of patients who are inadequate responders, lost response or are intolerant to conventional therapy or biologic treatment.

## *3.3. Uncertainties and limitations about favourable effects*

Slight decline of the symptomatic response through Week 44 was noted. To conclude whether the trend is temporal or persistent, the MAH has committed to provide the efficacy results of the QUASAR Maintenance study (final report expected in Q3 2028).

## *3.4. Unfavourable effects*

The safety profile of guselkumab was overall consistent with the known safety profile of guselkumab.

In the induction studies, most common adverse events were from the infections and infestations SOC, led by the COVID 19 and nasopharyngitis events.

The events of rash and pruritus showed some dose dependency in the QUASAR maintenance study. Upon review of the liver function test results for patients experiencing pruritus, only one case was identified with mild liver enzyme elevations with temporal association with pruritus. Hence, no product information is deemed necessary. The frequency of the ADR rash in the SmPC Section 4.8 is updated from uncommon to common.

The majority of malignancy cases occurred in patients with risk factors for the concerned malignancy.

ADT-status had an impact on AE frequencies in the induction and maintenance studies, as remarkably higher frequencies were observed in the ADT-failed group, might be the consequence of the more severe UC status of the ADT-failed subgroup rather than a negative safety effect.

MACE events including fatal ones occurred in the induction and maintenance periods of the QUASAR programme, as well as within the long-term safety data of QUASAR-M study. With the exception of QUASAR-M study, where one MACE event was observed in the guselkumab group, the event numbers were the same in the guselkumab and placebo groups. The MACE events were reported in patients concerned with CV risk factors. MACE is an important potential risk in the RMP and is monitored via routine and additional pharmacovigilance activities.

## 3.5. Uncertainties and limitations about unfavourable effects

In the maintenance study, the AE frequencies in the dose adjustment subpopulations were generally lower or similar to those in the two randomised guselkumab groups. However, the Guselkumab 100 mg Q8W - Guselkumab 200 mg Q4W subpopulation included only 19 patients, therefore it is hard to draw any firm conclusion from the observations in this guselkumab dose adjustment group.

There is limited safety data for the subpopulation above 65 years of age and very limited safety data for the subpopulation above 75 years. No patients above 85 years of age were included in the study. Use in patients ≥65 years of age is listed as missing information in the RMP.

## 3.6. Effects Table

**Table 58: Effects Table for Tremfya in UC (data cut-off: January 2023)**

| Effect | Short Description | Unit | Treatment (GUS) | Control (PBO) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Clinical remission | Week 12 | % | 22.6 (200 mg IV) | 7.9 (IV) | p<0.001 | Study CNTO1959UCO3001 |
| | Week 44 | % | 45.2 (100 mg)<br>50.0 (200 mg) | 18.9 | p<0.001 | |
| Corticosteroid-free clinical remission | Week 44 | % | 45.2 (100 mg)<br>48.9 (200 mg) | 18.4 | p<0.001 | |
| Endoscopic healing | Week 12 | % | 26.8 (200 mg IV) | 11.1 (IV) | p<0.001 | |
| | Week 44 | % | 49.5 (100 mg)<br>51.6 (200 mg) | 18.9 | p<0.001 | |
| Histologic-endoscopic mucosal healing | Week 12 | % | 23.5 (200 mg IV) | 7.5 (IV) | p<0.001 | |
| | Week 44 | % | 43.6 (100 mg)<br>47.9 (200 mg) | 16.8 | p<0.001 | |
| Symptomatic remission | Week 12 | % | 12.1 (200 mg IV) | 9.3 (IV) | Not significant | |
| | Week 44 | % | 70.2 (100 mg)<br>68.9 (200 mg) | 37.1 | p<0.001 | |
| **Unfavourable Effects** | | | | | | |
| Infections | Week 12 | % | 15.7 (200mg IV)<br>8.4 (400mg IV) | 14.0 | Most common infection: COVID-19. | QUASAR IS-1 and IS-2 Pooled and Maintenance Study |
| | Week 44 | % | 31.7 (serious: 0.5%) (100 mg)<br>31.1 (serious: 1.1) (200 mg) | 32.8 | | |
| ALT increased | Week 12 | % | 0.8 (200mg IV)<br>1.9 (400mg IV) | 0.3 | | |

| Effect | Short Description | Unit | Treatment (GUS) | Control (PBO) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| AST increased | Week 12 | % | 0.8 (200mg IV)<br>0.9 (400mg IV) | 0 | | |

Abbreviations:GUS 100 mg – Guselkumab 100 mg sc. Q8W, GUS 200 mg – guselkumab sc. 200 mg Q4W, PBO-Placebo

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The therapeutic effects seen on clinical remission and clinical response parameters of guselkumab in the treatment of UC are considered clinically relevant during the induction period. Early relief of UC symptoms rectal bleeding and stool frequency during the induction treatment are found clinically relevant for UC patients. Endoscopic healing and histologic-endoscopic healing and their maintenance during the maintenance study are indicative for a long-term positive outcome of the treatment of UC.

Lower efficacy was observed in the ADT-failure subgroup. However, according to the data from maintenance phase, clinical efficacy outcomes in this patient subgroup are still considered clinically relevant.

Slight decline in the symptomatic remission rate over time was observed during the maintenance study. To conclude whether the trend is temporal or persistent, the MAH has committed to provide the efficacy results of the QUASAR Maintenance study (final report expected in Q3 2028).

The majority of AEs observed during the QUASAR programme were known ADRs of guselkumab.

### 3.7.2. Balance of benefits and risks

Clinical response and remission observed during both the induction and maintenance phases are clinically relevant in the UC indication.

The safety profile of guselkumab is consistent with the known profile of the product.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

The overall benefit/risk balance of Tremfya is positive in the treatment of adult patients with moderately to severely active ulcerative colitis 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 CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Tremfya new strength, new route of administration and new pharmaceutical form is favourable in the following indication:

Ulcerative colitis

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Tremfya subject to the following conditions:

***Conditions or restrictions regarding supply and use***

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

***Conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

| Variations requested | | Type | Annexes affected |
|---|---|---|---|
| X.02.V | Annex I_2.(e) Change or addition of a new route of administration | Line Extension | I, IIIA, IIIB and A |
| 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, IIIA and IIIB |
| X.02.III | Annex I_2.(c) Change or addition of a new strength/potency | Line Extension | I, IIIA, IIIB and A |
| X.02.III | Annex I_2.(c) Change or addition of a new strength/potency | Line Extension | I, IIIA, IIIB and A |
| X.02.IV | Annex I_2.(d) Change or addition of a new pharmaceutical form | Line Extension | I, IIIA, IIIB and A |

Extension application to add a new pharmaceutical form (concentrate for solution for infusion), a new strength (200 mg) and a new route of administration (intravenous use) and to add a new strength of 200 mg for solution for injection (in pre-filled syringe / pre-filled pen) for subcutaneous use in the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment.

This application is grouped with a type II variation (C.I.6.a) to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 of the SmPC of the existing form 100 mg solution for injection are updated. The Package Leaflet and Labelling are updated in accordance. Version 10.4 of the RMP is adopted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to align the PI with QRD template version 10.4 and to introduce editorial changes to the PI.