Janssen-Cilag International N.V.
European Union Risk Management Plan
TREMFYA® (guselkumab)

Data lock point for current Risk Management Plan (RMP)	24 March 2024	Version number	12.1

Sign-off Date: 11 July 2025
Version Number: 12.1
Supersedes Version: 11.2
EDMS Number: EDMS-RIM-1673421

Qualified Person for Pharmacovigilance (QPPV) Name(s):	Dr Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The Marketing Authorization Holder (MAH) QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	12.1
Rationale for submitting an updated RMP	Version containing changes related to procedure EMA/VR/0000257669, as shown in RMP version 11.1: • Proposed addition of an alternative 100 mg pre-filled pen (PushPen). • Addition of the identifier "OnePress" to the approved 100 mg pre-filled pen.
Summary of significant changes in this RMP	<u>Product Overview: Pharmaceutical form and strength</u> Proposed addition of an alternative 100 mg pre-filled pen (PushPen). Addition of the identifier “OnePress” to the approved 100 mg pre-filled pen.

Other RMP Versions Under Evaluation

RMP Version Number	Submitted on	Procedure Number
10.3	03 February 2025	EMEA/X/0000248626
11.1	06 March 2025	EMA/VR/0000257541

Details of the Currently Approved RMP

Version number of last agreed RMP	11.2
Approved within procedure	EMEA/H/C/004271/II/0044
Date of approval (opinion date)	02 May 2025

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Part I. Product Overview

Active substance (INN or common name)	Guselkumab
Pharmacotherapeutic group (ATC Code)	L04AC16
Marketing Authorization Holder (MAH)	Janssen-Cilag International N.V.
Medicinal products to which the RMP refers	Guselkumab (TREMFYA®)
Invented name(s) in the European Economic Area (EEA)	TREMFYA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) to the interleukin (IL)-23 protein. Summary of mode of action Guselkumab is a human IgG1λ mAb that binds selectively to the IL-23 protein with high specificity and affinity through the antigen binding site. Interleukin-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets (eg, Th17 cells and Tc17 cells) and innate immune cell subsets. These represent sources of effector cytokines, including IL-17A, IL-17F, and IL-22, that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalize production of these cytokines. Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In patients with ulcerative colitis and Crohn's disease, levels of IL-23 are elevated in the colon tissue. In in vitro models, guselkumab inhibited the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptors and disrupting IL-23 mediated signaling, activation, and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease through blockade of the IL-23 cytokine pathway. Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, ulcerative colitis, and Crohn's disease. Guselkumab has demonstrated in vitro blocking of IL-23 and binding to CD64. These results indicate that guselkumab is able to neutralize IL-23 at the cellular source of inflammation. Important information about its composition Guselkumab is produced in Chinese hamster ovary cells by

	recombinant deoxyribonucleic acid (DNA) technology.
Reference to the product information	Module 1.3.1 Summary of Product Characteristics (SmPC), Labeling and Package Leaflet
Indication in the EEA	Current: *Plaque psoriasis* TREMFYA is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. *Psoriatic arthritis* TREMFYA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. *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. *Crohn's disease* TREMFYA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.
	Proposed: Not applicable.
Dosage in the EEA	Current: *Plaque psoriasis* The recommended dose of TREMFYA is 100 mg by subcutaneous (SC) injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. *Psoriatic arthritis* The recommended dose of TREMFYA is 100 mg by SC injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.

	Ulcerative colitis: The recommended induction dose is 200 mg administered by IV 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 SC injection every 8 weeks. Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by SC injection starting at Week 12 and every 4 weeks thereafter, may be considered. *Crohn's disease:* The recommended induction dose is 400 mg administered by SC injection 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 SC injection every 8 weeks. Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by SC injection starting at Week 12 and every 4 weeks thereafter may be considered.
	Proposed: Not applicable.
Pharmaceutical form and strength	Current: Solution for injection. Each pre-filled syringe and pre-filled pen (OnePress) contains 100 mg of guselkumab in 1 mL solution. Solution for injection. Each pre-filled syringe and pre-filled pen contains 200 mg of guselkumab in 2 mL solution. Concentrate for solution for infusion. Each vial contains 200 mg guselkumab in 20 mL solution.
	Proposed: Solution for injection. Each pre-filled pen (PushPen) contains 100 mg of guselkumab in 1 mL solution.
Is/will the product subject of additional monitoring in the European Union (EU)?	☑ **Yes** ☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication and Target Population

Indication: Psoriasis

Incidence:

Psoriasis is a common, chronic, relapsing, inflammatory skin disorder with a strong genetic basis. The extent and duration of the disease is highly variable from patient to patient. The most common type of psoriasis is plaque psoriasis, occurring in approximately 90% of cases (Boehncke 2015). Approximately 30% of patients with psoriasis also develop psoriatic arthritis (PsA; Boehncke 2015). Acute flares or relapses of plaque psoriasis may also evolve into more severe disease, with or without treatment, such as pustular or erythrodermic psoriasis, each occurring in fewer than 3% of patients (Lebwohl 2003). A survey from the Netherlands reported the incidence of erythrodermic psoriasis to be 0.9 per 100,000 inhabitants (Sigurdsson 2001). It has been estimated that erythrodermic psoriasis occurs once or more during the lifetime of 3% of people with plaque psoriasis (www.psoriasis.org).

A systematic review of the literature reported that the incidence of psoriasis in all ages ranged from 31.4 per 100,000 person-years (PY) in Russia to 521.1 per 100,000 PY in Germany (Parisi 2020). In an Italian national primary care database study that included adults with a first diagnosis of psoriasis between 2001 and 2005, the incidence of psoriasis ranged from 2.30 to 3.21 cases per 1,000 PY, with a slightly higher incidence in males (2.54-3.57 cases per 1,000 PY) than females (2.07-2.91 cases per 1,000 PY) (Vena 2010). In the United Kingdom (UK), the incidence of psoriasis using Clinical Practice Research Datalink data was reported as 129 per 100,000 in 2013 (Springate 2017). A nationwide study in Denmark that followed the entire adult population from 2003 to 2012 reported an incidence rate of 151.21 per 100,000 PY for 2012 (Egeberg 2017a).

Prevalence:

According to the Global Burden of Disease (GBD) study, there were approximately 65 million people with psoriasis in 2016 (GBD 2017).

Globally, it is estimated that psoriasis affected about 0.47% (95% uncertainty interval [UI] 0.15-1.25) of the population in 2017 (Parisi 2020). A systematic review of the literature reported that, regionally, the prevalence of psoriasis in the overall population ranged from 0.11% (95% UI 0.04-0.30) in East Asia, 1.58% (95% UI 0.50-5.73) in Australasia, and 1.52% (95% UI 0.87-2.74) in Western Europe (Parisi 2020). For other regions of Europe, the prevalence was 1.45% (95% UI 0.49-4.08; Central Europe) and 0.47% (95% UI 0.13-1.75; Eastern Europe) (Parisi 2020).

In Norway, the prevalence for psoriasis varied from 3.8% to 4.6% during the period from 2015 to 2020 (Solberg 2023).

Demographics of the Population in the Psoriasis Indication (Age and Sex) and Risk Factors for the Disease:

Psoriasis appears to occur most frequently in Northern European countries and is less common in populations of Eastern Asia. A weak correlation between geographic latitude and psoriasis prevalence has been reported (World Health Organization [WHO] 2016). Reports from nationally representative data in the United States (US) that stratified the sample by race among those between 20 and 59 years of age estimated the prevalence of psoriasis to be highest in Caucasians at 3.6%, followed by African Americans at 1.9%, Hispanics at 1.6%, and other races at 1.4% (Rachakonda 2014). There is lack of agreement in the published studies about variation by sex for psoriasis incidence (Parisi 2020). Some studies report a slightly higher incidence in males (Vena 2010).

The review by Parisi et al (2020) of psoriasis incidence at all ages reported that the incidence of psoriasis was higher in adults than in children, varying in adults from 30.3 per 100,000 PY (95% confidence interval [CI] 26.6-34.1) in Taiwan to 321.0 per 100,000 PY in Italy, and in children increasing with age from 13.5 per 100,000 PY (0-3 years old) to 53.1 per 100,000 PY (14-18 years old). In a systematic literature review, Iskandar (2021) reported a bimodal age pattern in the incidence of psoriasis, with peaks at 30 to 39 and 60 to 69 years of age. It was also reported that the prevalence of psoriasis increases with age (up to 60-70 years of age), after which it decreases, and that psoriasis presents slightly earlier in women than in men.

Several studies have demonstrated that genetics play a key role in the development of psoriasis. A higher prevalence of psoriasis has been found among first-degree relatives of psoriasis patients than in the general population (Eder 2015). Several genetic studies have suggested a strong association between psoriasis and human leukocyte antigen (HLA) class I genes, located in the major histocompatibility complex (Eder 2015). Psoriasis has also been associated with higher body mass index (BMI), lower physical activity, lower educational level, and smoking (Danielsen 2013). Infection has been proposed as a possible etiologic agent for certain subtypes of psoriasis, as acute episodes of guttate psoriasis have been associated with streptococcal infection, and the prevalence of psoriasis is increased in patients with human immunodeficiency virus (HIV; Setty 2007).

Main Existing Treatment Options:

Treatment for psoriasis is intended to interrupt the abnormal cycle that causes an increased production of skin cells, which can lead to reduced inflammation, reduced plaque formation, scale removal, and smoother skin. Therapy used to treat psoriasis include (Mayo Clinic 2019):

- Topical therapies (applied to the skin): This therapy includes creams and ointments such as topical corticosteroids (the most frequently prescribed medication for psoriasis), vitamin D analogs, anthralin, topical retinoids calcineurin inhibitors, salicylic acid, coal tar, and moisturizers. When the disease is severe, creams are likely to be combined with light therapy or oral medications.
- Light therapy (ie, exposing the skin to natural or artificial ultraviolet light).

- Systemic medications (oral or injected): Systemic forms of therapy are used for patients with moderate to severe psoriasis and include retinoids, MTX, immunomodulator drugs (including apremilast, cyclosporine, azathioprine [AZA]), biologics (including anti-tumor necrosis factor [TNF] alpha, anti-IL23 and anti-IL17 agents).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Because observational clinical trials generally include a treated population, it is difficult to describe the course of the disease in the untreated population and to differentiate the effects of treatment from the natural history of the disease. In a UK trial of patients between the ages of 25 and 64 years with at least 1 psoriasis diagnosis in the previous 2 years, 51.8% had mild psoriasis (≤2% body surface area [BSA] affected) (Yeung 2013). Moderate psoriasis (3%-10% BSA) and severe psoriasis (>10% BSA) were reported in 35.8% and 12.4% of patients, respectively. People with psoriasis may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions (NIAMS 2017). Severity of disease has also been shown to affect the prevalence of certain comorbidities, such as diabetes and cardiovascular (CV) disease. People with severe disease are also at greater risk of developing renal disease (odds ratio [OR]=1.83) and rheumatologic disease (OR=2.89) compared with those with mild disease (ORs of 0.97 and 2.01) for renal and rheumatologic disease, respectively (Yeung 2013).

A meta-analysis of 12 studies reporting all-cause or cause-specific mortality risk estimates in psoriasis patients compared with the general population or subjects free of psoriasis found that the pooled relative risks for all-cause mortality were 1.21 (95% CI 1.14-1.28) in psoriasis, 1.13 (95% CI 1.09-1.16) in mild psoriasis, and 1.52 (95% CI 1.35-1.71) in severe psoriasis (Dhana 2019). The pooled relative risk for CV mortality was the most prominent cause-specific mortality risk and was estimated to be 1.15 (95% CI 1.09-1.21) in psoriasis (Dhana 2019).

The increased mortality risk associated with severe psoriasis was also observed in a cohort study performed in a large UK medical records database (The Health Improvement Network [THIN]), which included data from 1994 to 2010 (Ogdie 2014). Among patients with psoriasis, the overall mortality rate (deaths per 1,000 PY) was 12.12. Among patients with psoriasis who were prescribed DMARDs, indicating more severe psoriasis, the mortality rate was 22.19. Among patients with psoriasis who were not prescribed DMARDs, the mortality rate was 11.92.

Important Comorbidities:

Comorbidities that frequently occur in patients with plaque psoriasis include metabolic disorders, obesity, hypertension, type 2 diabetes, non-alcoholic fatty liver disease, cardiac disorders, other autoimmune disease, depression or anxiety, non-melanoma skin cancers, and PsA (Pouplard 2013, Boehncke 2015, Yamazaki 2021, Hedemann 2022).

Indication: Psoriatic Arthritis

Incidence:

A meta-analysis of 28 international population-based observational studies reported a pooled incidence of PsA of 8.3 per 100,000 PY (95% CI 4.1-16.7). Interstudy heterogeneity was high, with incidence ranging from 3.0 to 41.3 cases per 100,000 PY (Scotti 2018).

The incidence of PsA in Denmark was reported as 19.8 per 100,000 population in 2011 (Egeberg 2017b) and 13 per 100,000 population in Finland for 2010 and 2014 (Muilu 2019).

Approximately 30% of patients with psoriasis also develop PsA (Gladman 2016). A systematic review of 10 studies of psoriasis patients reported PsA incidence rates ranging from 0.27 per 100 PY to 2.7 per 100 PY (Alinaghi 2019).

Prevalence:

A meta-analysis by Scotti et al (2018), reported a pooled prevalence of PsA of 133 per 100,000 population, ranging from 20 to 670 cases per 100,000 population. Interstudy heterogeneity was high, with some of the differences being explained by PsA detection criteria.

In a large, multinational, population-based survey of psoriasis and/or PsA patients conducted in 2005 in North America and Europe, the prevalence of psoriasis/PsA ranged from 1.4% to 3.3% (Lebwohl 2014). In this study, 79% of patients had psoriasis alone and 21% also had PsA. Other studies on the prevalence of PsA in patients with psoriasis have provided varying estimates ranging from 6% to 41% (Ogdie 2015).

One study used data from THIN, a large UK-based medical record database, to conduct a cross-sectional study. Among 4.8 million patients in the THIN database between 18 and 90 years of age, 9,045 patients had at least 1 medical code for PsA between 1994 and 2010, giving an overall prevalence of 0.19% (95% CI 0.185%-0.193%) (Ogdie 2013). In the study by Christophers et al (2010), for patients with psoriasis, PsA prevalence increased with time since psoriasis diagnosis, reaching 20.5% after 30 years.

Demographics of the Population in the PsA Indication and Risk Factors for the Disease:

The demographic profile of PsA is consistent with that of psoriasis. Overall, men and women are affected by PsA with equal frequency (Muilu 2019) and the average age of onset of PsA is 36 to 40 years of age (Gladman 2009). Prevalence by age and sex reported in the study based on data from the THIN database conducted by Ogdie et al (2013) is shown in the following table.

Table SI.1: Prevalence of Psoriatic Arthritis by Age and Sex

Age (years)	Men		Women		All	
	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)
18-29	316	0.05	353	0.05	669	0.05
30-39	916	0.17	819	0.16	1,735	0.16
40-49	1,157	0.29	952	0.26	2,109	0.28
50-59	1,115	0.36	1,092	0.36	2,207	0.36
60-69	675	0.31	733	0.32	1,408	0.31
70-80	334	0.23	380	0.20	714	0.21
80-90	75	0.12	128	0.10	203	0.11
All	**4,591**	**0.20**	**4,461**	**0.18**	**9,045**	**0.19**

PsA=psoriatic arthritis.

Risk Factors:

Having psoriasis is the single greatest risk factor for developing PsA, with those who have psoriasis with nail involvement being particularly at risk (Mayo Clinic 2021). Physical trauma, rubella vaccination, oral ulcers, infections that require antibiotic treatment, injuries, and occupations that involve lifting heavy weights have been associated with PsA (Gladman 2016); see also the PsA incidence and prevalence data above.

Studies have suggested that there is a high risk for PsA among first degree relatives of affected individuals (Mayo Clinic 2021). There is a genetic component, particularly with HLA class I alleles at the B and C loci (Gladman 2016).

Main Existing Treatment Options:

Treatment recommendations for PsA were developed by a task force of the European League Against Rheumatism (EULAR), as well as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment is aimed at reaching the target of remission or achieving minimal/low disease activity. Initial therapy for musculoskeletal manifestations of PsA includes non-steroidal anti-inflammatory drugs (NSAIDs). Traditional DMARDs such as MTX, sulfasalazine, and leflunomide are used when poor prognostic indicators are present. TNFα inhibitor therapy or other biologics (anti-IL-12/23 or anti-IL-17 agents) are considered when PsA signs and symptoms persist despite traditional treatment. Janus kinase inhibitors, such as tofacitinib and upadacitinib, may be considered in PsA patients with severe phenotypes (Caso 2023, Harkins 2023). Local injections of glucocorticoids can also be considered as adjunctive therapy (Coates 2016, Gossec 2016).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

PsA is a highly heterogeneous disorder which presents challenges in diagnosis and treatment. It may present with varying clinical features, several of which are observed in other conditions and the pattern of joint involvement is variable. Early inflammatory changes in PsA affect soft tissue and bone marrow and cannot be detected with the use of plain radiography. As the disease progresses, radiographic images may demonstrate changes which are similar to those observed in rheumatoid arthritis (McArdle 2018).

Mortality:

Several studies have reported mortality rates for PsA patients that are comparable to the general population. A systematic review of 10 studies did not reveal an increased mortality compared to the general population, with an RR of 1.12 (95% CI 0.96-1.30). For male patients, the all-cause mortality RR was 1.02 (95% CI 0.66–1.59). Mortality was higher in female patients, with an RR of 1.19 (95% CI 1.04–1.36) (Chaudhary 2023).

Important Comorbidities:

Comorbidities that occur in PsA patients include CV disease, metabolic syndrome, obesity, diabetes mellitus, dyslipidemia, inflammatory bowel disease, fatty liver disease, uveitis, kidney disease, infections, osteoporosis, depression, central sensitization syndrome, and gout (Perez-Chada 2020).

Indication: Ulcerative colitis

Incidence:

In a systematic review of the worldwide incidence of ulcerative colitis (UC) from 1990 to 2016, Ng (2017) found that the annual incidence of UC varied by geographic region, with estimates ranging from 0.97 to 57.9 per 100,000 PY in Europe, 8.8 to 23.14 per 100,000 PY in North America, 0.15 to 6.5 per 100,000 PY in Asia, and 0.19 to 6.76 per 100,000 PY in South America.

In a systematic review of the literature from 2010 to 2020, Zhao (2021) reported that the incidence of UC in Europe ranged between 2.4 to 44.0 per 100,000 PY. The highest incidence was reported in the Faroe Islands (44.0 per 100,000 PY), and the lowest incidence was found in Romania (2.4 per 100,000 PY).

For specific regions of Europe for the period from 1990 to 2016, the reported incidence of UC ranged from 0.97 to 11.9 per 100,000 PY in Eastern Europe, 1.7 to 57.9 per 100,000 PY in Northern Europe, 3.3 to 11.5 per 100,000 PY in Southern Europe, and 1.9 to 17.2 per 100,000 PY in Western Europe (Ng 2017).

A nationwide study that included all individuals in Denmark between 1980 and 2013 found that the incidence rate of UC increased from 10.7 (95% CI 10.4-11.0) per 100,000 PY from 1980 to 1989 to 18.6 (95% CI 18.0-19.2) per 100,000 PY from 2010 to 2013 (Lophaven 2017).

In the Netherlands, the incidence has been reported at 17.2 per 100,000 PY (de Groof 2016).

Two Swedish studies reported incidences of 20.0 (95% CI 16.1-23.9) per 100,000 population and 18.1 (95% CI 15.4-20.8) per 100,000 population (Sjöberg 2013, Eriksson 2017). Several studies showed an increase in incidence over time (Eriksson 2017, Lophaven 2017).

Prevalence:

In a systematic review of the worldwide prevalence of UC from 1990 to 2016, Ng (2017) found that the prevalence of UC varied by geographic region, with estimates ranging from 2.4 to 505.0 per 100,000 population in Europe, 139.8 to 286.3 per 100,000 population in North America, 4.6 to 106.2 per 100,000 population in Asia, and 4.7 to 44.3 per 100,000 population in South America. Another systematic review reported prevalence ranging from 4.9 to 505.0 per 100,000 population in Europe and 37.5 to 248.6 per 100,000 population in North America; prevalence was highest in Norway (505 per 100,000 population) and Canada (248 per 100,000 population) (Molodecky 2012).

The prevalence of UC ranged from 2.4 (Romania) to 432 (Scotland) per 100,000 population (Zhao 2021). For specific regions of Europe for the period from 1990 to 2016, prevalence estimates ranged from 2.42 to 340.0 per 100,000 population in Eastern Europe, 90.8 to 505.0 per 100,000 population in Northern Europe, 14.5 to 133.9 per 100,000 population in Southern Europe, and 43.1 to 412.0 per 100,000 population in Western Europe (Ng 2017).

Demographics of the Population in the UC Indication (Age and Sex) and Risk Factors for the Disease:

UC occurs at similar rates in both sexes until the age of 45, after which the rate increases in males (Zhao 2021). The incidence of UC has a bimodal age distribution, with a first peak in the second or third decade of life and a second peak between the ages of 50 and 80 years (Gajendran 2019). A regional study conducted in Spain reported the incidence rate for UC in women as 2.7 per 100,000 population and 5.1 per 100,000 population in men from 2007 to 2008 (Cueto Torreblanca 2017).

Risk Factors:

Risk factors for UC include age (disease onset is usually between 15 and 30 years); a family history of the disease (including a 4× increased risk in first degree relatives; there is concordance in monozygotic and dizygotic twins [18% and 7%, respectively]); urban living; recent *Salmonella*, *Clostridioides difficile*, or *Campylobacter* infection; tobacco cessation; soda consumption; being of Ashkenazi Jewish descent; and dietary intake of processed and high-fat foods (Gajendran 2019, Adams 2022, Le Berre 2023).

Main Existing Treatment Options:

The goal of treatment for UC is to attain mucosal healing with symptom control so that sustained steroid-free remission can be achieved and to prevent hospitalizations and surgeries. Treatment is dependent on disease severity (Adams 2022).

For the treatment of mild to moderate disease, 5-aminosalicylic acid therapies are recommended. First-line therapy for moderate to severe UC is biologics. Systemic corticosteroids are effective in inducing remission, but dosages and treatment duration should be limited due to well-recognized toxicities. Treatment options for inducing remission of moderate to severely active UC include TNFα antibodies, anti-integrin antibodies, anti-interleukin antibodies, Janus kinase inhibitors, and sphingosine-1-phosphate receptor modulators (Adams 2022, Bencardino 2023).

Surgery may be necessary in approximately 15% of patients with UC for treatment of fulminant or refractory disease (Adams 2022).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The natural course of UC is characterized by periods of flare alternating with periods of remission. The severity of flares and response to treatment vary among patients, can be hard to predict, and range from minor symptoms to life-threatening fulminant colitis that requires colectomy. During the course of the disease, extraintestinal manifestations, such as arthritis, uveitis, and pyoderma gangrenosum, are observed in up to 31% of patients (Cosnes 2011, Vavricka 2011). The majority of patients have a mild to moderate disease course, which is most active at diagnosis, followed by varying periods of remission or mild activity; the cumulative risk of relapse is 70% to 80% at 10 years. Almost 50% of patients require UC-related hospitalization (Fumery 2018). In general,

over a 10-year period, 50% to 55% of patients remit; approximately 37% follow a chronic, intermittent course; 6% develop a chronic continuous course; and 1% have a period of low activity followed by a severe increase (Fumery 2018). Approximately 20% to 30% of patients require a colectomy after 25 years of disease activity (Gajendran 2019).

Mortality:

No difference in mortality was observed in a meta-analysis published in 2007, which was based on 10 population-based studies in patients with UC compared with the general population (SMR 1.1; 95% CI 0.9–1.2) (Jess 2007). A population-based Finnish study also found no differences in overall mortality (SMR 0.90; 95% CI 0.77–1.06) (Manninen 2012). A nationwide register study including 21,964 IBD patients, also conducted in Finland, reported an SMR of 1.10 (95% CI 1.05-1.15) (Zhao 2021). A Swedish study reported an incidence of 16.5 per 1,000 PY (95% CI 16.2-16.9) and an HR of 1.4 (95% CI 1.4-1.5) for all-cause mortality in UC for the years 1964 to 2014 (Olén 2020). A Spanish study reported a mortality rate of 19.4 per 100,000 population in 2016 (Brunet 2018).

Patients with UC have increased mortality from pulmonary disease (SMR 1.24; 95% CI 1.02-1.46), CV disease (SMR 1.14; 95% CI 1.06–1.22), and cancers of the colon (SMR 1.90; 95% CI 1.38-2.5), rectum (SMR 1.79; 95% CI 1.14–2.69), and biliary tract (SMR 5.65; 95% CI 3.54–8.54), whereas mortality from alcohol-related deaths is decreased (SMR 0.54; 95% CI 0.39–0.71) (Zhao 2021).

Important Comorbidities:

Comorbidities that occur in patients with UC include small bowel or colorectal cancer; episcleritis; arthritis; hepatobiliary disorders; infections such as *Helicobacter pylori* and cytomegalovirus; celiac disease; pancreatic disease; obesity; CV conditions including venous thromboembolism and atherosclerosis; and anxiety and mood disorders (Román 2011, Burisch 2013).

Indication: Crohn's disease

Incidence:

A systematic review of the literature from 2010 to 2020 reported that the incidence of Crohn's disease (CD) in Europe ranged from 0.4 to 22.8 per 100,000 PY. The highest incidence of CD was reported in The Netherlands (22.8 per 100,000 PY), and the lowest incidence was reported in Moldova (0.4 per 100,000 PY) (Zhao 2021).

In a systematic review of the worldwide incidence of CD from 1990 to 2016, Ng (2017) reported that the annual incidence varied by geographic region, with estimates ranging from 0.0 to 15.4 per 100,000 PY in Europe, 0.06 to 8.4 per 100,000 PY in Asia, 6.3 to 23.82 per 100,000 PY in North America, and 0.0 to 3.5 per 100,000 PY in South America.

Generally, the incidence of CD increased in the Western world during the last 50 years of the twentieth century, including North America, Europe, Australia, and New Zealand (Aniwan 2017).

Prevalence:

The prevalence of CD ranged between 1.5 (Romania) to 331 (The Netherlands) per 100,000 population (Zhao 2021).

In a literature review that covered 1990 to 2016, estimates of the prevalence of CD ranged from 1.51 to 322 per 100,000 population in Europe, 1.05 to 53.1 per 100,000 population in Asia, 96.3 to 318.5 per 100,000 population in North America, and 0.9 to 41.4 per 100,000 population in South America (Ng 2017). For specific regions of Europe for this period, prevalence estimates ranged from 1.51 to 200 per 100,000 population in Eastern Europe, 24.0 to 262.2 per 100,000 population in Northern Europe, 4.5 to 137.17 per 100,000 population in Southern Europe, and 28.2 to 322.0 per 100,000 population in Western Europe (Ng 2017).

In the US, the prevalence of CD in adults (age over 17 years) was reported as 197.7 per 100,000 population (95% CI 195.8-199.6) (Ye 2020).

Demographics of the Population in the Crohn's Disease Indication and Risk Factors for the Disease:

A pooled analysis of studies conducted in Europe, North America, Australia, and New Zealand reported that the incidence rate of CD is lower in females than in males during childhood, but then increases in females compared with males in the 10- to 14-year age group; thereafter, it generally remains higher in females than in males (Shah 2018).

In the UK, the estimated prevalence for Crohn's disease in 2017 was 354 and 448 per 100,000 for males and females, respectively (King 2020).

The incidence of CD is higher in Ashkenazi Jews, urban populations, and in northern latitudes (Gajendran 2018). Peak incidence of CD is between 20 to 40 years (Zhao 2021).

Risk Factors:

Risk factors for CD include age younger than 30 years, being white or of Ashkenazi Jewish descent, having a close relative with the disease, and living in urban or industrialized areas. A low fiber high-fat diet, use of certain medications (such as antibiotics, NSAIDs, and oral contraceptives) (Adams 2022, Aniwan 2017) and history of appendectomy or tonsillectomy (Piovani 2019) are also risk factors for CD. The most important controllable risk factor is cigarette smoking (Mayo Clinic 2022).

Main Existing Treatment Options:

The goal of medical treatment of CD is to reduce the inflammation that triggers signs and symptoms of the condition and that may lead to long-term damage. It is also to improve long-term prognosis by limiting complications. In the best cases, treatment may lead to long-term remission. Drugs used to treat CD include:

- Anti-inflammatory drugs: These are often used as a first step in the treatment of CD. Examples include sulfasalazine, mesalamine, and corticosteroids.
- Immune system suppressors: These drugs reduce inflammation by suppressing the immune response. Sometimes, these drugs are used in combination. Examples include AZA, 6-mercaptopurine, MTX, cyclosporin, infliximab, adalimumab, and vedolizumab.
- Antibiotics: These drugs can reduce the amount of drainage and sometimes heal fistulas and abscesses in patients with CD. It is also believed that antibiotics reduce harmful intestinal bacteria that might suppress the intestine's immune system, triggering symptoms. Examples include metronidazole and ciprofloxacin.
- In addition to controlling inflammation, some medications may help to relieve signs and symptoms of the disease. Examples include antidiarrheals, laxatives, pain relievers, iron supplements, vitamin B 12 injections, and calcium and vitamin D supplements.

If lifestyle changes, drug therapy, or other treatments do not relieve the signs and symptoms of CD, surgery may be required to remove the damaged portion of the digestive tract, close fistulas, and drain abscesses (Mayo Clinic 2022). In Europe, the 1-year rate of major surgery in patients with CD ranged between 6% and 14%, increasing to between 12% to 27% at 5 years after diagnosis (Zhao 2021).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Crohn's disease begins gradually, becoming worse over time (NIDDK 2017). It is a chronic disease with a remitting and relapsing nature. At any given time, approximately half of all patients are in remission. Those who are in remission for 1 year have an 80% chance of remaining in remission in the subsequent year. Those who had active disease in the past year have a 70% chance of having active disease in the subsequent year. Overall, 13% of the patients have a relapse-free disease course, 20% of the patients have relapse every year, and 67% of patients have a

combination of years in relapse and years in remission within the first 8 years of initial diagnosis (Gajendran 2018).

Possible complications of the disease include intestinal obstruction, fistulas, abscesses, anal fissures, ulcers, malnutrition, and inflammation in other parts of the body. Patients with CD in the large intestine are more likely to develop colon cancer (NIDDK 2017). Additionally, approximately 25% to 46% of patients with CD experience extraintestinal manifestations (Hovde 2012). One study conducted in Hungary reported that the probability of developing more complicated disease in patients with adult-onset CD was 12.1%, 26.4%, and 37.5% after 1, 5, and 10 years of follow-up, respectively (Lovasz 2013). Similarly, 27.1% of patients with CD in Europe develop stricturing disease and 29.4% develop penetrating disease within 10 years of diagnosis (Burisch 2015).

Mortality:

Mortality in patients with CD is increased when compared with the general population, with a reported standardized mortality ratio (SMR) of 1.39 (95% CI 1.30–1.49). Regarding cause-specific mortality, a significantly increased risk of death from cancer, chronic obstructive pulmonary disease, gastrointestinal disease, and genitourinary disease has been observed in patients with CD (Zhao 2021). A Spanish study reported a mortality rate of 17.0 per 100,000 population in 2016 (Brunet 2018). A Swedish study with 984,330 person-years of follow-up reported a hazard ratio (HR) of 1.6 (95% CI 1.6-1.7) for all-cause mortality in adult-onset CD for the years 1964 to 2014 compared with the general population (Olén 2020).

A study in southeastern Norway followed all patients diagnosed with CD between 1990 and 1993 for 20 years (Hovde 2014). In this study, no differences between patients with CD and controls were found in overall mortality (HR=1.35, 95% CI 0.94-1.94). In total, 13.9% of patients in the CD group died compared with 12.7% of patients in the control group. There were no marked differences in deaths from gastrointestinal cancer, other cancers, or CV disease in the CD group compared with controls. No explanation for the possible difference from other studies was described.

Important Comorbidities:

Comorbidities that occur in patients with CD include colorectal cancer; hepatobiliary disorders; *Helicobacter pylori* infection; pancreatic disease; obesity; CV conditions, including venous thromboembolism and atherosclerosis; uveitis; nephrolithiasis; depression; anxiety; and bipolar disorder (Román 2011, Burisch 2013, Cury 2013, Bernstein 2019).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety program for guselkumab was designed in accordance with International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use (S6 [1997] and S6 [R1] [2011]) guidelines. Safety pharmacology evaluations (CV, respiratory, and central nervous system) were incorporated into the repeat-dose toxicology studies in accordance with ICH S7A (2000), and immunotoxicity evaluations were incorporated into the repeat-dose toxicology studies in accordance with ICH S8 (2005). A separate CV safety pharmacology study was also conducted with guselkumab. The reproductive toxicology program was conducted in the cynomolgus monkey (enhanced pre/postnatal development; ePPND) and guinea pig (female and male fertility) in accordance with ICH S5 (R2) guidelines (2005).

Guselkumab neutralizes human, cynomolgus monkey, and guinea pig IL-23, but does not neutralize rodent IL-23. Therefore, the cynomolgus monkey and guinea pig were selected as pharmacologically relevant species for the nonclinical safety testing of guselkumab.

No toxicologically significant findings were identified in the nonclinical safety studies conducted in cynomolgus monkeys and guinea pigs with guselkumab.

Key Safety Findings From Nonclinical Safety Pharmacology and Toxicology Studies

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
In the GLP repeat-dose toxicity study in cynomolgus monkeys, administration of guselkumab up to 50 mg/kg/week IV for 5 weeks (subchronic) or SC for 24 weeks (chronic) did not result in any guselkumab-related changes.	No toxicities due to the inhibition of IL-23 were identified in the nonclinical studies.
The doses and the dose regimens selected for the subchronic/chronic toxicology study in cynomolgus monkey (up to 50 mg/kg IV once weekly for one month or up to 50 mg/kg SC once weekly for 6 months) were sufficient to produce serum concentrations of guselkumab that greatly exceeded the concentrations required to neutralize IL-23 in this species. These dose regimens produced AUC exposures that were at least 23 times the maximum clinical exposures following a dose of 200 mg given IV.	
The guinea pig was selected to assess female and male fertility (see below). The guselkumab doses and dose frequency selected for both male and female fertility assessments also resulted in exposures that greatly exceeded the concentrations required to neutralize IL-23 in the guinea pig and were likewise in excess of clinical exposure levels. There were no effects observed on male or female fertility parameters after guinea pigs were	

Key Safety Findings	Relevance to Human Usage
subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly. In the male fertility study, the guselkumab dosing regimen produced AUC exposures that were 26 times higher than those in humans administered the 200 mg IV induction dose and 45 times the exposure relative to the 200 mg SC maintenance dose. In the female fertility study, the AUC exposures were 12 times the exposure in humans administered the 200 mg IV induction dose and 21 times the exposure relative to the 200 mg SC maintenance dose.	
Developmental toxicity	
Results from an ePPND toxicity study in pregnant cynomolgus monkeys demonstrated that weekly SC doses of 10 or 50 mg/kg guselkumab administered from gestation day (GD) 20-22 through approximately GD 160 were well tolerated. No maternal toxicity was observed, and no effects on fetal survival, infant growth, or development were noted through 6 months postpartum, indicating a no-observed-adverse-effect-level of 50 mg/kg/week for both maternal and developmental outcomes.	The cumulative preclinical data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development. The ePPND toxicity study conducted in cynomolgus monkeys demonstrated no maternal toxicity and no developmental abnormalities in the offspring. It was shown that fetuses are exposed to guselkumab transplacentally during the fetal period. This profile is expected to be similar in humans and is similar to that of endogenous immunoglobulin (IgG) antibodies. Because of this transfer, it is expected that infants from guselkumab-treated mothers will have guselkumab in their serum at birth and that IL-23 will be inhibited until the serum concentration decreases below a pharmacologically relevant level. The clinical relevance of exposure in human infants whose mothers were treated with guselkumab is unknown. Concentrations of guselkumab in milk samples of cynomolgus monkeys on After Birth Day 28 (ie, 28 days after birth) were below the lowest quantifiable concentration for the assay (ie, <0.20 μg/mL).
Genotoxicity	
Monoclonal antibodies are unlikely to be genotoxic because their large molecular size precludes them from diffusing into cells and interacting with DNA and other chromosomal materials, as detailed in ICHS6 (R1).	The weight of evidence suggests no increased risk for genotoxicity.

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
The risk of reduced tumor immune surveillance resulting in susceptibility to certain tumors (lymphomas and skin cancer) is a safety concern for immunomodulatory drugs in general. No tumors were detected in cynomolgus monkeys dosed with guselkumab for up to 6 months. Rodent 2-year carcinogenicity studies have not been conducted because this bioassay is a poor predictor of malignancy due to immune suppression (Bugelski 2010). Additionally, conduct of such studies was not considered as guselkumab is not cross-reactive in the rodent. Lastly, because of their molecular structure, mAbs are unlikely to interact with DNA. However, the possibility that an immune-suppressing mAb could support or induce proliferation through activation or inhibition of specific pathways cannot be entirely ruled out. Therefore, consistent with the ICHS6 (R1) guidance, a weight-of-evidence approach was conducted to evaluate the potential carcinogenic risk of guselkumab. This approach included a review of published information on class effects, detailed information on target biology and mechanism of action, in vitro data, data from mouse tumor models, data from chronic toxicity studies, and clinical data. It was concluded that the risk of malignancy associated with long-term inhibition of IL-23 following administration of guselkumab to humans is considered low, although it cannot be ruled out as a potential risk associated with modulation of IL-23 activity.	There is a theoretical risk of malignancy associated with administration of guselkumab based on clinical experience with other immunomodulatory drugs. The preponderance of evidence from the published literature (knockout mice where IL-23 is ablated and in some models following exogenously administered or overexpressed IL-23) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in mice deficient for IL-23 and p19 exposed to ultraviolet-B (UVB) radiation (Jantschitsch 2012). Therefore, based on the weight of evidence, the risk of malignancy associated with long-term inhibition of IL-23 following administration of guselkumab to humans is considered low but cannot be ruled out as a potential risk associated with modulation of IL-23 activity. Malignancy is considered an important potential risk for guselkumab.
Safety pharmacology	
CV safety pharmacology	
A CV safety pharmacology study was conducted to identify any potential effects of guselkumab on hemodynamic parameters and electrocardiographic activity in conscious, telemetered cynomolgus monkeys that received an intravenous (IV) bolus of 0.9% saline for injection on Day 1 (control), and 10 or 50 mg/kg guselkumab on Day 5. Treatment had no adverse effect on hemodynamic parameters (including systolic, diastolic, mean arterial pressure), QT, QT corrected using Bazett's formula (QTcB), and heart rate. There was no distribution of guselkumab or complementarity determining region-mediated binding to cardiac or skeletal myocytes following immunohistochemistry evaluation of heart and striated (skeletal) muscle tissue.	No adverse effects due to the inhibition of IL-23 were identified following the conduct of a CV safety pharmacology study or during the conduct of subchronic/chronic toxicity studies.

Key Safety Findings	Relevance to Human Usage
Hepatotoxicity	
No clinical pathology, gross, or histopathological findings in the liver were identified during general toxicity studies.	Nonclinical studies indicate no increased risk for hepatotoxicity.
Other toxicity-related information or data	
Infection	
In cynomolgus monkeys, no infections were observed following weekly treatment with guselkumab for 5-weeks by IV administration, and 24-weeks by SC administration or following a 3-month non-dosing recovery period when guselkumab was still present in the serum. Immune competence as assessed by T cell-dependent antibody response was unaltered. Interleukin-23 may contribute to immunity for a variety of bacterial and fungal pathogens as assessed in murine models of these infections (see summary of data in the published literature in Section SVII.3.1).	No infections were observed during toxicity studies conducted in cynomolgus monkeys (conducted by the MAH). However, as per the published murine data (see Section SVII.3.1), there is a theoretical risk that inhibition of IL-23 may increase the risk of infection. The literature in mice suggests that IL-23 is necessary for immunity to a variety of bacterial and fungal pathogens. Serious infection is considered an important potential risk for guselkumab.

Safety concerns from nonclinical data that have been confirmed or have not been adequately refuted by clinical data are listed in the following table.

Conclusion of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	Serious infection
	Malignancy
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The clinical development program for guselkumab includes trials in subjects with psoriasis, PsA, UC, CD, rheumatoid arthritis, palmoplantar pustulosis, hidradenitis suppurativa, and familial adenomatous polyposis, as well as in healthy subjects.

SIII.2. Clinical Trial Exposure

Guselkumab exposure data are presented for the psoriasis and PsA Phase 2 and Phase 3 trials listed below. Exposure to guselkumab is summarized in Table SIII.1 through Table SIII.8 by duration, by age and sex, by dose, and by variable stratifications relevant to the product (ie, ethnic origin). Exposure data are presented for 2 analysis sets from the psoriasis, PsA, UC, and CD Phase 2 and Phase 3 trials:

- Randomized, blinded clinical trials population (placebo-controlled periods).
- All clinical trials population, including blinded (placebo-controlled and active-comparator controlled) and open-label (uncontrolled) periods.

By design, subjects can receive up to 5 years of treatment with guselkumab in the Phase 3 psoriasis trials (CNTO1959PSO3001 and CNTO1959PSO3002) and up to 1 year or 2 years in the Phase 3 PsA trials (CNTO1959PSA3001 and CNTO1959PSA3002, respectively). Subjects can receive up to 5 years of treatment with guselkumab in the Phase 2b/3 UC trial (CNTO1959UCO3001). Subjects can receive up to 5 years of treatment with guselkumab in the Phase 2/3 CD trial CNTO1959CRD3001 and up to 2 years of treatment in the Phase 3 CD trial CNTO1959CRD3004.

Exposure Methodology for Psoriasis and PSA Trials

The duration of exposure was calculated based on the time from the administration of the first dose of guselkumab to the last dose of guselkumab in the analysis period and extending through the time point at which the next dose would have been administered (ie, an additional 4 or 8 weeks, depending on the dosing interval). The duration of follow-up was calculated based on the time from the first dose of guselkumab to the date of the last visit or last contact, whichever was later in the analysis period.

Exposure Methodology for UC Trial

Duration of treatment exposure within an analysis period is calculated as the time interval from the first administration to the last administration of guselkumab within the analysis period and includes 12 weeks of drug exposure after the last guselkumab dose, which accounts for approximately 5 half-lives of guselkumab. Participants for whom the duration between the first and last guselkumab administrations was at least 12 weeks were defined as having an exposure of at least 6 months. Participants for whom the duration between the first and last guselkumab administrations was at least 36 weeks were defined as having an exposure of at least 1 year.

Duration of study follow-up is the time interval from first administration of study intervention to last study visit or last study contact, whichever is later in an analysis period.

Exposure Methodology for CD Trials

Duration of treatment exposure within an analysis period is calculated as the time interval from the first administration to the last administration of guselkumab within the analysis period and includes 12 weeks of drug exposure after the last guselkumab dose, which accounts for approximately 5 half-lives of guselkumab. Participants for whom the duration between the first and last guselkumab administrations was at least 12 weeks were defined as having an exposure of at least 6 months. Participants for whom the duration between the first and last guselkumab administrations was at least 36 weeks were defined as having an exposure of at least 1 year. Duration of study follow-up is the time interval from first administration of study intervention to last study visit or last study contact, whichever is later in an analysis period.

Exposure in Randomized, Blinded Clinical Trials Population

For the randomized, blinded clinical trials population, exposure data are presented from the placebo-controlled periods of the clinical trials in adults with psoriasis, PsA, UC, and CD listed below. Only subjects who received guselkumab from first administration of study agent were included in the analyses. Subjects who received no guselkumab through the end of the placebo-controlled period or who first received placebo or active comparator and then crossed over to receive guselkumab were excluded from the guselkumab exposure analyses. The placebo-controlled periods for each of the trials included in the analyses are specified below.

Psoriasis:

- CNTO1959PSO2001, a Phase 2 randomized, placebo- and active- comparator-controlled, parallel group, multicenter dose-ranging trial of guselkumab in subjects with moderate to severe plaque psoriasis (Week 0 to Week 16)
- CNTO1959PSO3001, a Phase 3 trial to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis (Week 0 to Week 16)
- CNTO1959PSO3002, a Phase 3 trial to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis with randomized withdrawal and retreatment (Week 0 to Week 16)
- CNTO1959PSO3006, a Phase 3 trial to evaluate the efficacy and safety of guselkumab delivered via a SelfDose device in subjects with moderate to severe plaque psoriasis (Week 0 to Week 16)

Psoriatic Arthritis:

- CNTO1959PSA2001, a Phase 2 trial to evaluate the efficacy and safety of guselkumab in subjects with active PsA (Week 0 to Week 24)
- CNTO1959PSA3001, a Phase 3 trial evaluating the efficacy and safety of guselkumab in subjects with PsA who were previously treated with biologic anti-TNFα agents (Week 0 to Week 24)

- CNTO1959PSA3002, a Phase 3 trial evaluating the efficacy and safety of guselkumab in subjects with PsA (Week 0 to Week 24)

Ulcerative Colitis:

- CNTO1959UCO3001, a Phase 2b/3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active UC that includes a placebo-controlled Phase 2b dose-ranging study (Induction Study 1) and a placebo-controlled Phase 3 induction study (Induction Study 2) (both Week I-0 to Week I-12)

Crohn's Disease:

- CNTO1959CRD3001, a Phase 2/3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active CD that includes a Phase 2 dose-ranging study (GALAXI I) and two identical Phase 3 confirmatory studies (GALAXI 2 and GALAXI 3) (Week 0 to 12)
- CNTO1959CRD3004, a Phase 3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active CD (Week 0 to Week 12)

Table SIII.1 through Table SIII.4 present exposure data from the randomized, blinded clinical trials population (placebo-controlled period) of the Phase 2 and Phase 3 psoriasis, PsA, UC, and CD trials noted above by duration of treatment, age and sex, dose, and race.

Table SIII.1: Exposure by Duration (Randomized, Placebo-controlled, Blinded Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Duration of exposure (at least)		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1044	246
12 weeks[b]	1044	246
Ulcerative colitis trials[c]		
Subjects treated with guselkumab	659	154
12 weeks[b]	659	154
Psoriasis trials[d]		
Subjects treated with guselkumab	1092	339
16 weeks[e]	927	290
Psoriatic arthritis trials[f]		
Subjects treated with guselkumab	848	390
24 weeks[g]	769	357
All trials[a,c,d,f]		
Subjects treated with guselkumab	3643	1129
12 weeks[b]	1703	400
16 weeks[e]	927	290
24 weeks[g]	769	357

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Subjects received at least one dose of guselkumab in crohn's disease and ulcerative colitis trials.
[c] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[d] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[e] The duration between the first and last guselkumab administration was at least 8 weeks in psoriasis trials.
[f] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).
[g] The duration between the first and last guselkumab administration was at least 16 weeks for subjects who received guselkumab 100 mg q8w and at least 20 weeks for subjects who received guselkumab 100 mg q4w in psoriatic arthritis trials.

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Table SIII.2: Exposure by Age Group and Sex (Randomized, Placebo-controlled, Blinded Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Men		Women	
	Subjects	Subject-years of Follow-up	Subjects	Subject-years of Follow-up
Age group				
Crohn's disease trials[a]				
Subjects treated with guselkumab	605	142	439	103
<45 years	464	109	291	69
45 – <65 years	127	30	120	28
≥65 years	14	3	28	6
Ulcerative Colitis trials[b]				
Subjects treated with guselkumab	370	86	289	68
<45 years	215	50	185	43
45 – <65 years	127	29	90	21
≥65 years	28	6	14	3
Psoriasis trials[c]				
Subjects treated with guselkumab	778	242	314	97
<45 years	414	129	150	46
45 – <65 years	325	101	146	45
≥65 years	39	12	18	6
Psoriatic arthritis trials[d]				
Subjects treated with guselkumab	457	210	391	180
<45 years	208	96	164	76
45 – <65 years	223	103	203	93
≥65 years	26	12	24	11
All trials[a,b,c,d]				
Subjects treated with guselkumab	2210	680	1433	449
<45 years	1301	384	790	235
45 – <65 years	802	263	559	188
≥65 years	107	34	84	26

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[c] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[d] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).

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Table SIII.3: Exposure by Dose (Randomized, Placebo-controlled, Blinded Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Dose of exposure		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1044	246
400 mg SC	230	54
200 mg IV	668	158
600 mg IV	73	17
1200 mg IV	73	16
Ulcerative Colitis trials[b]		
Subjects treated with guselkumab	659	154
200 mg IV	548	128
400 mg IV	111	26
Psoriasis trials[c]		
Subjects treated with guselkumab	1092	339
5 mg SC	41	13
15 mg SC	41	13
50 mg SC	42	13
100 mg SC	927	287
200 mg SC	41	13
Psoriatic arthritis trials[d]		
Subjects treated with guselkumab	848	390
100 mg SC	848	390
All trials[a,b,c,d]		
Subjects treated with guselkumab	3643	1129
5 mg SC	41	13
15 mg SC	41	13
50 mg SC	42	13
100 mg SC	1775	678
200 mg SC	41	13
400 mg SC	230	54
200 mg IV	1216	286
400 mg IV	111	26
600 mg IV	73	17
1200 mg IV	73	16

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[c] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[d] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).

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Table SIII.4: Exposure by Racial Origin (Randomized, Placebo-controlled, Blinded Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Race		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1044	246
White	786	185
Black or African American	13	3
Asian	201	47
American Indian or Alaskan native	2	0
Native Hawaiian or other Pacific Islander	5	1
Other	0	0
Multiple	0	0
Unknown	0	0
Not reported	37	9
Missing	0	0
Ulcerative Colitis trials[b]		
Subjects treated with guselkumab	659	154
White	467	109
Black or African American	7	2
Asian	149	35
American Indian or Alaskan native	1	0
Native Hawaiian or other Pacific Islander	1	0
Other	0	0
Multiple	2	0
Unknown	0	0
Not reported	32	7
Missing	0	0
Psoriasis trials[c]		
Subjects treated with guselkumab	1092	339
White	913	284
Black or African American	16	5
Asian	138	43
American Indian or Alaskan native	3	1
Native Hawaiian or other Pacific Islander	4	1
Other	13	4
Multiple	5	2
Unknown	0	0
Not reported	0	0
Missing	0	0
Psoriatic arthritis trials[d]		
Subjects treated with guselkumab	848	390
White	819	377
Black or African American	0	0
Asian	28	13
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	1	0
Other	0	0
Multiple	0	0
Unknown	0	0
Not reported	0	0
Missing	0	0
All trials[a,b,c,d]		
Subjects treated with guselkumab	3643	1129
White	2985	955
Black or African American	36	9
Asian	516	138

Table SIII.4: Exposure by Racial Origin (Randomized, Placebo-controlled, Blinded Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
American Indian or Alaskan native	6	2
Native Hawaiian or other Pacific Islander	11	3
Other	13	4
Multiple	7	2
Unknown	0	0
Not reported	69	16
Missing	0	0

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[c] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[d] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).

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Exposure in the All Clinical Trials Population

For the all clinical trials population, guselkumab exposure data are presented for the entire reporting period, including both blinded (placebo-controlled and active-comparator controlled) and open-label (uncontrolled) periods of the clinical trials in adults with psoriasis, PsA, UC, and CD listed below. All subjects who received guselkumab at any time during the trials were included in the analyses, including those subjects who first received placebo or active comparator and then crossed over to receive guselkumab. For subjects who first received placebo or active comparator and then crossed over to receive guselkumab, only data on or after the first dose of guselkumab were included. The reporting periods for each of the trials included in the analyses are specified below.

Psoriasis

- CNTO1959PSO2001, a Phase 2 randomized, placebo- and active- comparator-controlled, parallel group, multicenter dose-ranging trial of guselkumab in subjects with moderate to severe plaque psoriasis (Week 0 to Week 52)
- CNTO1959PSO3001, a Phase 3 trial to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis (Week 0 to Week 264)
- CNTO1959PSO3002, a Phase 3 trial to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis with randomized withdrawal and retreatment (Week 0 to Week 264)
- CNTO1959PSO3003, a Phase 3 trial to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis and an inadequate response to ustekinumab (Week 16 to Week 60)
- CNTO1959PSO3006, a Phase 3 trial to evaluate the efficacy and safety of guselkumab delivered via a SelfDose device in subjects with moderate to severe plaque psoriasis (Week 0 to Week 40)
- CNTO1959PSO3009, a Phase 3 trial to evaluate the efficacy of guselkumab compared with secukinumab in subjects with moderate to severe plaque psoriasis (Week 0 to Week 56)

Psoriatic Arthritis

- CNTO1959PSA2001, a Phase 2 trial to evaluate the efficacy and safety of guselkumab in subjects with active PsA (Week 0 to Week 56)
- CNTO1959PSA3001, a Phase 3 trial evaluating the efficacy and safety of guselkumab in subjects with PsA who were previously treated with biologic anti-TNFα agents (Week 0 to Week 60)
- CNTO1959PSA3002, a Phase 3 trial evaluating the efficacy and safety of guselkumab in subjects with PsA (Week 0 to Week 112)

Ulcerative Colitis:

- CNTO1959UCO3001, a Phase 2b/3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active UC that includes a Phase 2b dose-ranging study (Induction Study 1) and a Phase 3 induction study (Induction Study 2) as well as the Phase 3 Maintenance Study (Week I-0 to Week M-44)

Crohn's Disease:

- CNTO1959CRD3001, a Phase 2/3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active CD that includes a Phase 2 dose-ranging study (GALAXI I) and two identical Phase 3 confirmatory studies (GALAXI 2 and GALAXI 3) (Week 0 to 48)
- CNTO1959CRD3004, a Phase 3 trial to assess the efficacy and safety of guselkumab in subjects with moderately to severely active CD (Week 0 to Week 48)

Table SIII.5 through Table SIII.8 present guselkumab exposure data from the all clinical trials population (blinded and open-label periods combined) of the Phase 2 and Phase 3 psoriasis, PsA, UC, and CD trials noted above by duration, age and sex, dose, and race.

Table SIII.5: Exposure by Duration (All Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Duration of exposure (at least)		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1089	934
6 months[b]	1010	911
1 year[c]	901	837
Ulcerative colitis trials[d]		
Subjects treated with guselkumab	897	767
6 months[b]	678	688
1 year[c]	508	574
Psoriasis trials[e]		
Subjects treated with guselkumab	2711	8110
6 months[f]	2601	8071
1 year[g]	2255	7791
2 years[h]	1545	7012
3 years[i]	1482	6865
4 years[j]	1393	6568
5 years[k]	950	4717
Psoriatic arthritis trials[l]		
Subjects treated with guselkumab	1229	1871
6 months[m]	1181	1853
1 year[n]	968	1685
2 years[o]	408	884
All trials[a,d,e,l]		
Subjects treated with guselkumab	5926	11682
6 months[b,f,m]	5470	11524
1 year[c,g,n]	4632	10887
2 years[h,o]	1953	7897
3 years[i]	1482	6865
4 years[j]	1393	6568
5 years[k]	950	4717

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[b] The duration between the first and last guselkumab administration was at least 12 weeks in crohn's disease and ulcerative colitis trials.
[c] The duration between the first and last guselkumab administration was at least 36 weeks in crohn's disease and ulcerative colitis trials.
[d] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[e] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[f] The duration between the first and last guselkumab administration was at least 16 weeks in psoriasis trials.
[g] The duration between the first and last guselkumab administration was at least 40 weeks in psoriasis trials.
[h] The duration between the first and last guselkumab administration was at least 88 weeks in psoriasis trials.
[i] The duration between the first and last guselkumab administration was at least 136 weeks in psoriasis trials.
[j] The duration between the first and last guselkumab administration was at least 184 weeks in psoriasis trials.
[k] The duration between the first and last guselkumab administration was at least 232 weeks in psoriasis trials.
[l] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).
[m] The duration between the first and last guselkumab administration was at least 16 weeks for subjects who received guselkumab 100 mg q8w and at least 20 weeks for subjects who received guselkumab 100 mg q4w in psoriatic arthritis trials.
[n] The duration between the first and last guselkumab administration was at least 44 weeks for subjects who received guselkumab 100 mg q8w and at least 48 weeks for subjects who received guselkumab 100 mg q4w in

psoriatic arthritis trials.
[o] The duration between the first and last guselkumab administration was at least 96 weeks for subjects who received guselkumab 100 mg q8w and at least 100 weeks for subjects who received guselkumab 100 mg q4w in psoriatic arthritis trials.

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Table SIII.6: Exposure by Age Group and Sex (All Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Men		Women	
	Subjects	Subject-years of Follow-up	Subjects	Subject-years of Follow-up
Age group				
Crohn's disease trials[a]				
Subjects treated with guselkumab	635	546	454	389
<45 years	489	425	302	261
45 – <65 years	132	111	121	103
≥65 years	14	9	31	24
Ulcerative Colitis trials[b]				
Subjects treated with guselkumab	517	430	380	337
<45 years	301	253	250	224
45 – <65 years	176	146	115	98
≥65 years	40	31	15	16
Psoriasis trials[c]				
Subjects treated with guselkumab	1908	5811	803	2299
<45 years	967	3016	405	1197
45 – <65 years	834	2509	340	981
≥65 years	107	286	58	121
Psoriatic arthritis trials[d]				
Subjects treated with guselkumab	640	1001	589	870
<45 years	293	469	234	355
45 – <65 years	313	480	315	468
≥65 years	34	52	40	47
All trials[a,b,c,d]				
Subjects treated with guselkumab	3700	7788	2226	3895
<45 years	2050	4163	1191	2037
45 – <65 years	1455	3246	891	1650
≥65 years	195	379	144	208

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[b] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[c] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[d] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).

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Table SIII.7: Exposure by Dose (All Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Dose of exposure		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1089	934
100 mg SC	471	419
200 mg SC	532	478
400 mg SC	274	235
200 mg IV	668	586
600 mg IV	73	58
1200 mg IV	73	54
Ulcerative Colitis trials[b]		
Subjects treated with guselkumab	897	767
100 mg SC	197	208
200 mg SC	505	504
200 mg IV	786	666
400 mg IV	111	102
Psoriasis trials[c]		
Subjects treated with guselkumab	2711	8110
5 mg SC	41	35
15 mg SC	41	39
50 mg SC	42	40
100 mg SC	2546	7957
200 mg SC	41	38
Psoriatic arthritis trials[d]		
Subjects treated with guselkumab	1229	1871
100 mg SC	1229	1871
All trials[a,b,c,d]		
Subjects treated with guselkumab	5926	11682
5 mg SC	41	35
15 mg SC	41	39
50 mg SC	42	40
100 mg SC	4443	10456
200 mg SC	1078	1020
400 mg SC	274	235
200 mg IV	1454	1252
400 mg IV	111	102
600 mg IV	73	58
1200 mg IV	73	54

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[b] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[c] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[d] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).

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Table SIII.8: Exposure by Racial Origin (All Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
Race		
Crohn's disease trials[a]		
Subjects treated with guselkumab	1089	934
White	811	699
Black or African American	16	12
Asian	216	184
American Indian or Alaskan native	2	2
Native Hawaiian or other Pacific Islander	5	3
Other	0	0
Multiple	0	0
Unknown	0	0
Not reported	39	35
Missing	0	0
Ulcerative Colitis trials[b]		
Subjects treated with guselkumab	897	767
White	639	540
Black or African American	10	9
Asian	200	177
American Indian or Alaskan native	1	1
Native Hawaiian or other Pacific Islander	2	2
Other	0	0
Multiple	2	2
Unknown	0	0
Not reported	43	36
Missing	0	0
Psoriasis trials[c]		
Subjects treated with guselkumab	2711	8110
White	2313	6719
Black or African American	47	128
Asian	300	1102
American Indian or Alaskan native	6	10
Native Hawaiian or other Pacific Islander	7	24
Other	27	91
Multiple	11	34
Unknown	0	0
Not reported	0	0
Missing	0	0
Psoriatic arthritis trials[d]		
Subjects treated with guselkumab	1229	1871
White	1185	1819
Black or African American	0	0
Asian	41	50
American Indian or Alaskan native	0	0
Native Hawaiian or other Pacific Islander	1	1
Other	0	0
Multiple	0	0
Unknown	0	0
Not reported	0	0
Missing	2	1
All trials[a,b,c,d]		
Subjects treated with guselkumab	5926	11682

Table SIII.8: Exposure by Racial Origin (All Clinical Trials Population); Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Subjects	Subject-years of Follow-up
White	4948	9777
Black or African American	73	149
Asian	757	1514
American Indian or Alaskan native	9	13
Native Hawaiian or other Pacific Islander	15	30
Other	27	91
Multiple	13	36
Unknown	0	0
Not reported	82	71
Missing	2	1

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[b] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[c] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[d] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 1:	**Is pregnant, nursing, or planning a pregnancy**
Reason for being an exclusion criterion	Per ICH guidance, pregnant women are generally excluded from clinical trials. It is unknown whether guselkumab is excreted in human milk.
Included as missing information?	Pregnancy: Yes Nursing: No
Rationale (if not included as missing information)	Nursing: Information from nonclinical studies, postmarketing experience, and the published literature has not suggested any risks of clinical significance to infants exposed to guselkumab via breast milk. A decision should be made whether to discontinue treatment or abstain from initiating treatment with TREMFYA, taking into account the benefit of breast-feeding to the child and the benefit of TREMFYA therapy to the woman (SmPC Section 4.6, Fertility, pregnancy and lactation).
Criterion 2:	**Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients**
Reason for being an exclusion criterion	Treatment with immunomodulatory agents may increase the risk of hypersensitivity reactions.
Included as missing information?	No.
Rationale (if not included as missing information)	Serious hypersensitivity to guselkumab or to any of its excipients is listed as a contraindication in the SmPC. Subjects who have known allergies, hypersensitivity, or intolerance to guselkumab or its excipients are likely to react again upon re-exposure. Hypersensitivity and anaphylaxis are listed as adverse drug reactions in the SmPC (Section 4.8, Undesirable effects).
Criterion 3:	**Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection; chronic chest infection (eg, bronchiectasis); recurrent urinary tract infection; recurrent pyelonephritis or chronic nonremitting cystitis; fungal infection (mucocutaneous candidiasis); or open, draining, or infected skin wounds or ulcers**
Criterion 4:	**Has or has had herpes zoster within the 2 months before screening**
Reason for being an exclusion criterion	Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection, including dissemination of herpes zoster infection.
Included as missing information?	No.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Serious infection is an important potential risk for TREMFYA. Clinically important active infection (eg, active tuberculosis [TB]) is a contraindication to TREMFYA use (SmPC Section 4.3, Contraindications). Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated (SmPC Section 4.4, Special Warnings and Precautions for Use).
Criterion 5:	**Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug or has had a Bacillus-Calmette-Guérin (BCG) vaccination within 12 months of screening**
Reason for being an exclusion criterion	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination.
Included as missing information?	No.
Rationale (if not included as missing information)	Guidance regarding the administration of vaccines is provided in SmPC Section 4.4 (Special Warnings and Precautions for Use), including the following: Prior to initiating therapy with TREMFYA, completion of all appropriate immunizations should be considered according to current immunization guidelines. Live vaccines should not be used concurrently in patients treated with TREMFYA. Before live viral or live bacterial vaccination, treatment with TREMFYA should be withheld for at least 12 weeks after the last dose and can be resumed at least 2 weeks after vaccination.
Criterion 6:	**Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of an NMSC that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration, or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration)**
Criterion 7:	**Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly**
Reason for being an exclusion criterion	Treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy.
Included as missing information?	No.
Rationale (if not included as missing information)	Although the risk of malignancy associated with long-term inhibition of IL-23 following administration of TREMFYA is considered to be low based on a weight-of-evidence approach, malignancy cannot be ruled out as a potential risk associated with modulation of IL-23 activity. Data in psoriasis, PsA, UC, and CD clinical trials have not shown an increased risk of malignancy in subjects treated with guselkumab. However, based on the theoretical risk of malignancy for all immunomodulatory drugs, malignancy is considered an important potential risk for TREMFYA.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 8:	**Is currently undergoing or has previously undergone allergy immunotherapy for a history of anaphylactic reactions**
Reason for being an exclusion criterion	At the time the Phase 3 clinical trials protocols were written, there was concern about a theoretical risk of decreased efficacy of allergy immunotherapy associated with IL-23 blockade.
Included as missing information?	No.
Rationale (if not included as missing information)	An evaluation of the theoretical risk of decreased efficacy of allergy immunotherapy associated with IL-23 blockade led to the conclusion that this is no longer a risk of treatment with guselkumab; therefore, current or previous allergy immunotherapy for a history of anaphylactic reactions is no longer an exclusion criterion.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The guselkumab clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with long latency, or those caused by prolonged exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Although pregnant women were excluded from clinical trials, exposure to guselkumab during pregnancy occurred in the clinical development program. As of 01 November 2023, 120 pregnancies were reported in guselkumab clinical trials, including 63 pregnancies in female subjects exposed to guselkumab and 57 pregnancies in female partners of male subjects exposed to guselkumab.
Breast-feeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with CV impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Although subjects with some of these comorbidities may have been eligible for the clinical development program at the discretion of the investigator, no exposure data are available.
Population with relevant different ethnic origin	Most subjects included in clinical trials were white. The predominant racial origin of the remaining subjects was Asian. When psoriasis, PsA, UC, and CD trials are considered separately, the proportions of subjects of different racial origin were similar across indications (see Section SIII.2, Table SIII.8).
Subpopulations carrying relevant genetic polymorphisms	Not included (ie, not identified) in the clinical development program.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Elderly	A total of 339 subjects who were ≥65 years of age (165 in psoriasis trials, 74 in PsA trials, 55 in UC trials, and 45 in CD trials) received guselkumab (see Section SIII.2, Table SIII.6).

Summary of Safety Concerns Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy
	Use in patients ≥65 years of age
	Long-term safety of guselkumab

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

TREMFYA was approved in the EU on 10 November 2017 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The recommended dose for guselkumab is 100 mg[1] to be given as SC injection at Week 0, Week 4, and every 8 weeks thereafter. Assuming that all patients are compliant with their treatment, 8 SC injections, or 800 mg, is equal to 1 person-year for the first year. Cumulative exposure to TREMFYA since launch, by region, is presented below in Table SV.1.

SV.1.2. Exposure

Based on the [redacted] milligrams distributed worldwide from launch through 30 June 2023, the estimated cumulative exposure to guselkumab is 407,104 PY.

Table SV.1: Cumulative Exposure to Guselkumab (Launch through 30 June 2023)

Region	Indication	Proportion of Sales (%)	Total Milligrams	Person-Years
European Union[a]	PsO	96	[redacted]	102,491
	PsA	4		4,270
Subtotal		***100***		***106,761***
United States	PsO	94	[redacted]	185,660
	PsA	6		11,850
Subtotal		***100***		***197,510***
Rest of World	PsO	*100*	[redacted]	***102,833***
Worldwide Total[b]				**407,104**

Key: PsA=psoriasis arthritis; PsO=psoriasis

[a] The United Kingdom is no longer a part of the European Union and has been grouped under rest of world from January 2021 onwards.

[b] The product was first distributed in July 2017.

[1] There is a second dosing regimen approved for the PsA indication (100 mg SC q4w), and this would result in a total of 13 doses per year. Considering the approval of the PsA indication, the limited number of markets with authorizations that include the q4w dosing regimen, and market data that indicate very limited use of the alternative dosing regimen, the 100 mg q8w regimen was used to calculate estimated patient exposure for all markets and all indications.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

As a class, therapeutic mAbs are not associated with abuse or dependence. The pharmaceutical and pharmacokinetic/pharmacodynamic characteristics of guselkumab are not characteristic of drugs with high dependence potential (eg, rapid onset/short-acting active substances). Therefore, the potential for the misuse of TREMFYA for illegal purposes is unlikely.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

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

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Medical Dictionary for Regulatory Activities (MedDRA) versions 23.0 (psoriasis and PSA) and 26.0 (UC and CD) were used to classify the clinical trial adverse event (AE) information that is summarized in this Module.

For tables SVII.1 through SVII.3, refer to Section SIII.2 for a description of subjects/data included in the guselkumab groups in the randomized, blinded clinical trials population/period and all clinical trials population/period. Note: If a subject first received active comparator as part of the randomized, blinded clinical trials population and then crossed over to receive guselkumab, data prior to the first guselkumab dose were excluded from the analyses.

For the placebo groups, only data during treatment with placebo were included. Data on or after the first dose of guselkumab, or any active comparator, were excluded from the placebo groups.

Tables are not presented if no events related to a particular important risk were reported in the completed and ongoing clinical trials described in Section SIII.2.

Important Potential Risk – Serious Infection

Potential Mechanisms:

Studies performed in mice deficient in IL-23p19 expression suggest that IL-23 may contribute to immunity to bacterial and fungal pathogens including, but not limited to the following: *Klebsiella pneumoniae* (Happel 2005), *Cryptococcus neoformans* (Kleinschek 2006), *Candida albicans* (Acosta-Rodriguez 2007; Kagami 2010), *Listeria monocytogenes* (Meeks 2009), *Helicobacter pylori* (Horvath 2012), *Pneumocystis carinii* (Rudner 2007), and Influenza A and *Staphylococcus aureus* co-infection (Kullberg 2006). However, the ability of these models to predict infection risk upon pharmacological IL-23 inhibition in humans has not been established. No IL-23-specific genetic deficiency has been identified in humans; however, individuals who are genetically deficient for IL-12/23p40 or the beta 1 chain of the IL-12 receptor β1 are functionally deficient in both IL-12 and IL-23 pathway signaling. These individuals show normal resistance to ubiquitous viruses; fungi; gram-positive and gram-negative bacteria; and common opportunistic protozoa. However, they demonstrate susceptibility to certain infections, including weakly virulent mycobacterial infections, BCG, environmental *Mycobacteria* species, recurring *Salmonella* species infections, recurrent or systemic *Candida*, *Paracoccidioides*, *Histoplasma*, and *Toxoplasma gondii* infections (Acosta-Rodriguez 2007; de Beaucoudrey 2010). The relative contribution of IL-12 and IL-23 in immunity to *Mycobacteria* or *Salmonella* species is unknown.

The role of IL-23, including the implications for its inhibition or loss of function on infectious disease, was recently summarized by Teng et al (2015).

Evidence Source(s) and Strength of Evidence:

Nonclinical data in mice suggest that blockade of IL-23 may predispose patients to infection.

Although serious infections were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of serious infection in patients treated with guselkumab.

Characterization of the Risk – Data:

Table SVII.1: Important Potential Risk - Serious Infections in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Avg duration of follow-up (weeks)	12.3	44.8	12.2	44.6	16.2	156.1	24.0	79.4	16.2	102.9
Frequency[i]	3 (0.3%)	12 (1.1%)	3 (0.5%)	17 (1.9%)	3 (0.3%)	60 (2.2%)	4 (0.5%)	26 (2.1%)	13 (0.4%)	115 (1.9%)
Guselkumab vs Placebo[j]	0.3% vs 0.0%	-	0.5% vs 0.5%	-	0.3% vs 0.2%	-	0.5% vs 0.7%	-	0.4% vs 0.4%	-
Odds ratio (95% CI)	-	-	0.917 (0.105, 11.023)	-	1.320 (0.106, 69.416)	-	0.660 (0.111, 4.530)	-	0.978 (0.346, 3.143)	-
Seriousness/outcomes										
Was Serious	3 (0.3%)	12 (1.1%)	3 (0.5%)	17 (1.9%)	3 (0.3%)	60 (2.2%)	4 (0.5%)	26 (2.1%)	13 (0.4%)	115 (1.9%)
Resulted in Death	0	0	0	0	0	0	0	0	0	0
Not recovered/not resolved	0	1 (0.1%)	0	0	0	2 (0.1%)	0	1 (0.1%)	0	4 (0.1%)
Recovering/resolving	0	1 (0.1%)	0	0	0	1 (<0.1%)	1 (0.1%)	2 (0.2%)	1 (<0.1%)	4 (0.1%)
Recovered with sequelae	0	0	1 (0.2%)	1 (0.1%)	0	3 (0.1%)	0	3 (0.2%)	1 (<0.1%)	7 (0.1%)
Recovered/resolved	3 (0.3%)	10 (0.9%)	2 (0.3%)	16 (1.8%)	3 (0.3%)	54 (2.0%)	3 (0.4%)	20 (1.6%)	11 (0.3%)	100 (1.7%)
Unknown	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0
Severity										
Mild	0	0	0	0	0	3 (0.1%)	0	0	0	3 (0.1%)
Moderate	3 (0.3%)	8 (0.7%)	2 (0.3%)	9 (1.0%)	2 (0.2%)	28 (1.0%)	4 (0.5%)	16 (1.3%)	11 (0.3%)	61 (1.0%)

Table SVII.1: Important Potential Risk - Serious Infections in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Severe	0	4 (0.4%)	1 (0.2%)	8 (0.9%)	1 (0.1%)	29 (1.1%)	0	10 (0.8%)	2 (0.1%)	51 (0.9%)
Missing	0	0	0	0	0	0	0	0	0	0

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[c] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[d] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[e] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[f] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[g] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).
[h] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).
[i] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk; the subject is counted only once regardless of the number of events or the number of occurrences.
[j] Denominators for the Placebo groups are:
Crohn’s Disease trials - Controlled Portions (N=340)
Ulcerative Colitis trials - Controlled Portions (N=403)
Psoriasis trials - Controlled Portions (N=480)
Psoriatic arthritis trials - Controlled Portions (N=421)
All trials - Controlled Portions (N=1644)
Note: Adverse events in crohn’s disease and ulcerative colitis trials are coded using MedDRA version 26.0. Adverse events in psoriasis and psoriatic arthritis trials are coded using MedDRA Version 23.0.

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Characterization of the Risk – Discussion:

Serious infections occurred infrequently in subjects treated with guselkumab, with a frequency similar to placebo during the placebo-controlled periods. In the all clinical trials population, a total of 1.9% of the guselkumab-treated subjects had serious infections.

Events of serious infection have been reported in patients treated with TREMFYA in the postmarketing setting.

Risk Factors and Risk Groups:

Risk factors for the development of serious infection include clinically significant metabolic and endocrine disorders such as diabetes, obesity, thyroid disorders, CV disorders, and renal and hepatic disorders; advanced age; and the concomitant use of corticosteroids, other biologics (including TNFα inhibitors), and other immunosuppressants.

Tuberculosis

The most common risk factors for the development of TB include conditions that weaken the immune system (eg, advanced age, HIV infection), alcohol abuse, malignancy, corticosteroids or other immunosuppressive drugs such as MTX, connective tissue disease, renal failure, diabetes, and pregnancy.

Exposure to TB is also a risk factor for the development of TB and patients who were born or lived in countries considered by the WHO to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or who have traveled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of TB or who had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.

Preventability:

TREMFYA is contraindicated in patients with clinically important active infections (eg, active TB; SmPC Section 4.3, Contraindications).

The SmPC (Section 4.4; Special Warnings and Precautions for Use) addresses preventability of serious infections by addressing immunizations, screening for TB infections, and by providing guidance regarding patients who develop an infection while being treated with TREMFYA.

Impact on the Risk-benefit Balance of the Product:

The impact of serious infection on the individual patient may be significant. Patients who develop infections may have a more severe course due to use of TREMFYA. The risk of serious infection must be carefully weighed against the benefit conferred by use of TREMFYA.

Public Health Impact:

The public health impact of serious infection during treatment with TREMFYA is not known.

Annex 1 MedDRA Term:

System organ class (SOC): Infections and infestations.

Important Potential Risk – Malignancy

Potential Mechanisms:

A weight-of-evidence approach was utilized to determine the potential for carcinogenicity following long-term antagonism of IL-23. This includes evidence from the toxicity studies conducted in cynomolgus monkeys and clinical trials in humans that indicate no increased risk for malignancy. Furthermore, the preponderance of evidence from the published literature (knockout models where IL-23 is ablated and in some models following exogenously administered or overexpressed IL-23) suggests that a risk for malignancy may actually be reduced in the setting of IL-23 inhibition. However, conflicting data from a limited number of studies in mouse models and from photocarcinogenicity experiments point to an increased risk of malignancy in IL-23p19-deficient mice exposed to UVB radiation. Therefore, while the risk for malignancy associated with long-term inhibition of IL-23 following administration of TREMFYA to humans is considered low, it cannot be ruled out as a potential risk associated with inhibition of IL-23 activity.

Evidence Source(s) and Strength of Evidence:

No increased risk for malignancy was observed following the conduct of a 5-week IV (subchronic) and a 24-week SC (chronic) study with a 3-month recovery of guselkumab in cynomolgus monkeys conducted by the MAH. Although there are no validated models for carcinogenicity evaluations in cynomolgus monkeys, neoplasia has been observed in this species following repeated administration of other immunosuppressive drugs indicated in the treatment of psoriasis. Most data in the published literature pertaining to models of IL-23 ablation suggest that blockade of IL-23 may actually reduce the risk of carcinogenesis. A limited number of studies in the literature present conflicting data supporting an increased risk of malignancy in mice deficient for IL-23 and p19 exposed to UVB radiation.

Although malignancies have been reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of malignancy in patients treated with guselkumab.

Characterization of the Risk – Data:

Table SVII.2: Important Potential Risk - Malignancies in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Avg duration of follow-up (weeks)	12.3	44.8	12.2	44.6	16.2	156.1	24.0	79.4	16.2	102.9
Frequency[i]	1 (0.1%)	4 (0.4%)	2 (0.3%)	5 (0.6%)	1 (0.1%)	62 (2.3%)	2 (0.2%)	4 (0.3%)	6 (0.2%)	75 (1.3%)
Guselkumab vs Placebo[j]	0.1% vs 0.0%	-	0.3% vs 0.0%	-	0.1% vs 0.0%	-	0.2% vs 0.2%	-	0.2% vs 0.1%	-
Odds ratio (95% CI)	-	-	-	-	-	-	0.993 (0.052, 58.716)	-	2.710 (0.328, 124.750)	-
Seriousness/outcomes										
Was Serious	0	1 (0.1%)	0	2 (0.2%)	0	29 (1.1%)	1 (0.1%)	1 (0.1%)	1 (<0.1%)	33 (0.6%)
Resulted in Death	0	0	0	0	0	3 (0.1%)	0	0	0	3 (0.1%)
Not recovered/not resolved	0	0	0	0	1 (0.1%)	22 (0.8%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	23 (0.4%)
Recovering/resolving	0	1 (0.1%)	0	2 (0.2%)	0	2 (0.1%)	0	0	0	5 (0.1%)
Recovered with sequelae	0	1 (0.1%)	0	0	0	0	0	0	0	1 (<0.1%)
Recovered/resolved	1 (0.1%)	2 (0.2%)	2 (0.3%)	3 (0.3%)	0	34 (1.3%)	1 (0.1%)	3 (0.2%)	4 (0.1%)	42 (0.7%)
Unknown	0	0	0	0	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Missing	0	0	0	0	0	0	0	0	0	0
Severity										
Mild	1 (0.1%)	2 (0.2%)	0	0	1 (0.1%)	16 (0.6%)	0	0	2 (0.1%)	18 (0.3%)
Moderate	0	0	2 (0.3%)	4 (0.4%)	0	27 (1.0%)	0	2 (0.2%)	2 (0.1%)	33 (0.6%)

Table SVII.2: Important Potential Risk - Malignancies in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Severe	0	2 (0.2%)	0	1 (0.1%)	0	19 (0.7%)	2 (0.2%)	2 (0.2%)	2 (0.1%)	24 (0.4%)
Missing	0	0	0	0	0	0	0	0	0	0

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[c] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[d] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[e] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[f] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[g] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).
[h] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).
[i] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk; the subject is counted only once regardless of the number of events or the number of occurrences.
[j] Denominators for the Placebo groups are:
Crohn’s Disease trials - Controlled Portions (N=340)
Ulcerative Colitis trials - Controlled Portions (N=403)
Psoriasis trials - Controlled Portions (N=480)
Psoriatic arthritis trials - Controlled Portions (N=421)
All trials - Controlled Portions (N=1644)
Note: Adverse events in crohn’s disease and ulcerative colitis trials are coded using MedDRA version 26.0. Adverse events in psoriasis and psoriatic arthritis trials are coded using MedDRA Version 23.0.

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Characterization of the Risk – Discussion:

Malignancies occurred infrequently among subjects treated with guselkumab and placebo during the placebo-controlled periods. In the all clinical trials population, a total of 1.3% of the guselkumab-treated subjects had malignancies.

Events of malignancy have been reported in patients treated with TREMFYA in the postmarketing setting.

Risk Factors and Risk Groups:

Among psoriasis patients, an increased risk of solid cancers appears to be related to alcohol use and cigarette smoking. Exposure to psoralen + ultraviolet-A (PUVA) radiation and immunosuppressants (including cyclosporin and possibly MTX) has been associated with squamous cell carcinoma in psoriasis patients (Pouplard 2013, Vaengebjerg 2020).

There does not appear to be an increased risk of malignancy among patients with psoriatic arthritis (Vaengebjerg 2020).

Patients with inflammatory bowel disease (IBD), including UC and CD, are at an increased risk of developing gastrointestinal malignancies such as colorectal cancer (Bopanna 2017, Wijnands 2021) and extraintestinal malignancies such as hepatobiliary cancers (Zhao 2021) and melanoma (Singh 2014). The risk of colorectal cancer in patients with UC appears to be related to extent of UC disease, presence of low-grade dysplasia, strictures, primary sclerosing cholangitis, and post-inflammatory polyps (Wijnands 2021). The risks of prostate cancer, uterine cervical cancer, and thyroid cancer are increased in patients with UC but not in patients with CD (Cao 2018, Ge 2020, Kim 2023). Patients with CD are at an increased risk of developing hematologic and lung cancers (Zhao 2021).

Cigarette smoking has been shown to have a protective effect against the development and severity of UC, while smokers with CD have a worse disease course (Lakatos 2007). Alcohol consumption may contribute to increased concentration of proinflammatory mediators, leading to a worsening of IBD symptoms (Kuźnicki 2021).

General risk factors for malignancy include increasing age, lifestyle factors (such as alcohol and tobacco use and obesity), family history of cancer, and certain environmental exposures.

Preventability:

Predictability and preventability of the development of malignancy is not known. Protection from ultraviolet exposure (either solar or from tanning beds) and avoidance of cigarette smoking, and alcohol use may decrease the risk of developing a cutaneous malignancy.

Impact on the Risk-benefit Balance of the Product:

The impact of malignancy on the individual patient can vary from minimal to potentially significant. The risk of malignancy must be carefully weighed against the benefits conferred by use of TREMFYA.

Public Health Impact:

The public health impact of malignancy during treatment with TREMFYA is not known.

Annex 1 MedDRA Term:

SOC: Neoplasms benign, malignant, and unspecified (including cysts and polyps).

Important Potential Risk – Serum Sickness

Potential Mechanisms:

Serum sickness is a type of hypersensitivity reaction which can occur several days after exposure to an antigen (eg, following mAb treatment).

Evidence Source(s) and Strength of Evidence:

Although an infrequent occurrence, serum sickness has been reported in the published literature in association with the use of other mAb therapies.

Characterization of the Risk

No cases of serum sickness have been reported in clinical trials to date. Serum sickness has been reported in patients treated with guselkumab in the postmarketing setting. The potential impact of serum sickness on the individual patient can vary from minimal to clinically significant (including death).

Risk Factors and Risk Groups:

Not known.

Preventability:

The predictability and preventability of serum sickness with administration of TREMFYA is not known. Early recognition and diagnosis of serum sickness and initiation of appropriate treatment can minimize the impact on the patient.

TREMFYA is contraindicated in patients with serious hypersensitivity to the active substance or to any of the excipients (SmPC Section 4.3, Contraindications). If a serious hypersensitivity reaction occurs, administration of TREMFYA should be discontinued immediately and appropriate therapy initiated (SmPC Section 4.4, Special Warnings and Precautions for Use).

Impact on the Risk-benefit Balance of the Product:

At present there is no information to suggest any impact on the risk benefit balance of the product. The SmPC and Patient Leaflet (PL) provide information to the prescriber and patient on how to manage the risk.

Public Health Impact:

The public health impact of serum sickness reactions during treatment with TREMFYA is not known.

Annex 1 MedDRA Term:

Preferred Term: Serum sickness.

Important Potential Risk – Major Adverse Cardiovascular Events (MACE)

Potential Mechanisms:

There is no known mechanistic basis for the development of MACE with blockade of IL-23.

The role of the IL-12, IL-23, and IL-17 cytokine cascade in the development and progression of coronary artery disease is described in the published literature. Some mouse model work has been conducted and clinical data from investigational research are emerging. Overall, the majority of studies conducted to date (including in vivo data in nonclinical models, as well as ex vivo and in vitro data) point to a potential role for inhibition of IL-23 in slowing or reversing coronary artery disease progression (Abbas 2015; Ávalos 2012; Langrish 2005; Yan 2012; Zhang 2014). Furthermore, no CV risks were identified in the context of the 5-week/24-week study or the targeted CV safety pharmacology study in cynomolgus monkeys (see Module SII). Taken together, the weight of the preclinical evidence does not support an increased risk of CV events in the setting of IL-23 blockade with guselkumab.

The effects of guselkumab on blood pressure and weight were evaluated in the Phase 3 psoriasis trials and no impact was identified.

Evidence Source(s) and Strength of Evidence:

Evidence for an increased background risk of CV disease (ie, heart attack, stroke, and death related to heart attack and stroke) in patients with psoriasis (including PsA) is cited in the published literature.

There is conflicting evidence of an increased background risk of CV disease (ie, heart attack, stroke, and death related to heart attack and stroke) in patients with inflammatory bowel disease (including UC and CD) in the published literature.

Although MACE were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of MACE in patients treated with guselkumab.

Characterization of the Risk – Data:

Table SVII.3: Important Potential Risk - Investigator-Reported MACE (Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke) in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Avg duration of follow-up (weeks)	12.3	44.8	12.2	44.6	16.2	156.1	24.0	79.4	16.2	102.9
Frequency[i]	0	2 (0.2%)	2 (0.3%)	3 (0.3%)	1 (0.1%)	26 (1.0%)	2 (0.2%)	4 (0.3%)	5 (0.1%)	35 (0.6%)
Guselkumab vs Placebo[j]	0.0% vs 0.0%	-	0.3% vs 0.5%	-	0.1% vs 0.0%	-	0.2% vs 0.2%	-	0.1% vs 0.2%	-
Odds ratio (95% CI)	-	-	0.610 (0.044, 8.455)	-	-	-	0.993 (0.052, 58.716)	-	0.752 (0.146, 4.847)	-
Seriousness/outcomes										
Was Serious	0	1 (0.1%)	2 (0.3%)	3 (0.3%)	1 (0.1%)	26 (1.0%)	2 (0.2%)	4 (0.3%)	5 (0.1%)	34 (0.6%)
Resulted in Death	0	0	1 (0.2%)	1 (0.1%)	0	3 (0.1%)	0	0	1 (<0.1%)	4 (0.1%)
Not recovered/not resolved	0	0	0	0	0	0	0	0	0	0
Recovering/resolving	0	0	0	0	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Recovered with sequelae	0	0	0	0	0	4 (0.1%)	1 (0.1%)	3 (0.2%)	1 (<0.1%)	7 (0.1%)
Recovered/resolved	0	2 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.1%)	18 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.1%)	23 (0.4%)
Unknown	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0
Severity										
Mild	0	0	0	0	0	0	0	0	0	0
Moderate	0	2 (0.2%)	0	0	0	7 (0.3%)	2 (0.2%)	3 (0.2%)	2 (0.1%)	12 (0.2%)

Table SVII.3: Important Potential Risk - Investigator-Reported MACE (Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke) in Clinical Trials; Subjects Treated with Guselkumab Across Indications in Phase 2 and Phase 3 Trials

	Crohn's Disease Trials		Ulcerative Colitis Trials		Psoriasis Trials		Psoriatic Arthritis Trials		All Clinical Trials	
	Placebo-controlled, Clinical Trials Population[a] (N=1044)	All Clinical Trials Population[b] (N=1089)	Placebo-controlled, Clinical Trials Population[c] (N=659)	All Clinical Trials Population[d] (N=897)	Placebo-controlled, Clinical Trials Population[e] (N=1092)	All Clinical Trials Population[f] (N=2711)	Placebo-controlled, Clinical Trials Population[g] (N=848)	All Clinical Trials Population[h] (N=1229)	Placebo-controlled, Clinical Trials Population[a,c,e,g] (N=3643)	All Clinical Trials Population[b,d,f,h] (N=5926)
Severe	0	0	2 (0.3%)	3 (0.3%)	1 (0.1%)	19 (0.7%)	0	1 (0.1%)	3 (0.1%)	23 (0.4%)
Missing	0	0	0	0	0	0	0	0	0	0

[a] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-12) and CNTO1959CRD3004 (Week 0-12).
[b] Crohn's disease trials include subjects treated with guselkumab in CNTO1959CRD3001 (Week 0-48) and CNTO1959CRD3004 (Week 0-48; including placebo crossover subjects).
[c] Ulcerative colitis trials include subjects treated with guselkumab in CNTO1959UCO3001 Induction Study 1 and Induction Study 2 (Week I-0 to I-12).
[d] Ulcerative colitis trials include subjects treated with guselkumab (including placebo crossover subjects) in CNTO1959UCO3001 Induction Study 1, Induction Study 2 and Maintenance Study (Week I-0 to Week M-44).
[e] Psoriasis trials include subjects treated with guselkumab in CNTO1959PSO2001 (Week 0-16), CNTO1959PSO3001 (Week 0-16), CNTO1959PSO3002 (Week 0-16), and CNTO1959PSO3006 (Week 0-16).
[f] Psoriasis trials include subjects treated with guselkumab (including placebo crossover and active comparator crossover subjects) in CNTO1959PSO2001 (Week 0-52), CNTO1959PSO3001 (Week 0-264), CNTO1959PSO3002 (Week 0-264), CNTO1959PSO3003 (Week 16-60), CNTO1959PSO3006 (Week 0-40), and CNTO1959PSO3009 (Week 0-56).
[g] Psoriatic arthritis trials include subjects treated with guselkumab in CNTO1959PSA2001 (Week 0-24, early escape subjects Week 0-16), CNTO1959PSA3001 (Week 0-24) and CNTO1959PSA3002 (Week 0-24).
[h] Psoriatic arthritis trials include subjects treated with guselkumab (including placebo crossover) in CNTO1959PSA2001 (Week 0-56), CNTO1959PSA3001 (Week 0-60) and CNTO1959PSA3002 (Week 0-112).
[i] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk; the subject is counted only once regardless of the number of events or the number of occurrences.
[j] Denominators for the Placebo groups are:
Crohn's Disease trials - Controlled Portions (N=340)
Ulcerative Colitis trials - Controlled Portions (N=403)
Psoriasis trials - Controlled Portions (N=480)
Psoriatic arthritis trials - Controlled Portions (N=421)
All trials - Controlled Portions (N=1644)
Note: Adverse events in crohn's disease and ulcerative colitis trials are coded using MedDRA version 26.0. Adverse events in psoriasis and psoriatic arthritis trials are coded using MedDRA Version 23.0.
Note: MACE identified by clinical review.

[tsfcv01.rtf] [PROD/xcp_immunology/cnto1959_rmp/dbr_rmp_core11/re_eu_version11_1/tsrisk01.sas] 13DEC2024, 07:51

Characterization of the Risk – Discussion:

Major adverse cardiovascular events occurred infrequently among subjects treated with guselkumab and placebo during the placebo-controlled periods. In the all clinical trials population, a total of 0.6% of the guselkumab-treated subjects had MACE.

MACE have also been reported in patients treated with TREMFYA in the postmarketing setting.

Risk Factors and Risk Groups:

The risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, advanced age, male sex, obesity, and family history. Patients with psoriasis have been shown to be at increased risk for CV events (ie, MACE, defined as CV death, nonfatal myocardial infarction, or nonfatal stroke) compared with the general population (Neimann 2006). Literature suggests psoriasis may be an independent risk factor due to the high inflammatory burden of psoriatic disease (Gelfand 2006; Gelfand 2009; Kimball 2009; Mehta 2010). Additionally, at least some CV risk factors occur more frequently in the psoriasis population compared with the general population. Specifically, these CV risk factors include pre-existing MACE conditions; uncontrolled or poorly controlled concomitant diseases such as diabetes, hypertension, hyperlipidemia, and obesity; and patient characteristics such as smoking (Augustin 2010; Kimball 2009). Of these, the association between psoriasis and dyslipidemia is less clear, with some studies showing that patients with psoriasis have significant dyslipidemia while others do not show a correlation (Yim 2017).

Notably, patients with severe psoriasis are more likely to demonstrate CV risk factors such as obesity, diabetes, and hypertension compared with those with no or mild psoriasis (Neimann 2006; Yim 2017).

Patients with IBD have not been shown to be at increased risk for CV events (ie, MACE, defined as CV death, nonfatal myocardial infarction, or nonfatal stroke) compared with the general population (Gill 2021, Osterman 2011) and IBD is not considered an independent cardiovascular risk factor (Massironi 2023). However, both UC and CD have been shown to be independently associated with an increased risk of acute myocardial infarction (Aniwan 2018, Alayo 2023, Sun 2018, Panhwar 2019, Kristensen 2013) and IBD may be an independent risk factor due to the high inflammatory burden of IBD (Bhardwaj 2023, Feng 2017, Wu 2017).

Additionally, CV risk factors vary considerably among the IBD population compared with the general population. Patients with IBD have lower rates of hypertension and lower lipid levels but elevated rates of diabetes when compared with the general population (Bigeh 2020). C-reactive protein (Alayo 2023) and fibrinogen (Alkim 2011) have also been shown to be elevated in the IBD population.

Preventability:

The preventability of CV disease is based upon the modification of known risk factors. A relationship between MACE and guselkumab has not been established.

Impact on the Risk-benefit Balance of the Product:

There is evidence for an increased background risk of CV disease in patients with psoriasis (including PsA), and patients may experience debilitating myocardial infarction, stroke, or death. Patients with psoriasis (including PsA) require vigilance in adequate treatment of CV risk factors.

There is conflicting evidence for an increased background risk of CV disease in patients with IBD (including UC and CD). Patients with IBD require vigilance in adequate treatment of CV risk factors.

Patients are not considered at further CV risk from use of TREMFYA beyond that related to the population risk.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

SOC: Cardiac disorders.

SVII.3.2. Presentation of the Missing Information

Missing information: Exposure during pregnancy

Evidence source: Women who were pregnant or planning a pregnancy were excluded from the guselkumab clinical development program.

It is not known whether guselkumab affects a developing fetus.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development (SmPC Section 4.6, Fertility, Pregnancy and Lactation).

Population in need of further characterization: Pregnant women

Missing information: Use in patients ≥65 years of age

Evidence source: There is limited safety information on use in patients ≥65 years of age from the guselkumab clinical development program and postmarketing surveillance.

Population in need of further characterization: Patients ≥65 years of age

Missing information: Long-term safety of guselkumab

Evidence source: TREMFYA was initially approved on the basis of clinical trial data up to Week 52 in moderate to severe plaque psoriasis. The long-term safety profile of guselkumab has been investigated in the Phase 3 trials in psoriasis (CNTO1959PSO3001, CNTO1959PSO3002) and in PsA (CNTO1959PSA3002). Long-term safety was comparable to that observed in the placebo-controlled study periods. Long-term safety, including in patients with UC and CD, is being further investigated in the other additional pharmacovigilance activities described in Part III.

Population in need of further characterization: Patients receiving long-term treatment with guselkumab.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of 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

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Serious infection	Topic of interest Targeted Follow-up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections
Malignancy	TOI TFUQ for Malignancies (including lymphoma, second and secondary malignancies)
Serum sickness	Topic of Interest Questionnaire (TOIQ) for Hypersensitivity and Anaphylactic Reaction
Major adverse cardiovascular events (MACE)	TOI TFUQ for Cardiovascular Events

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Not applicable	Not applicable	Not applicable

III.2. Additional Pharmacovigilance Activities

Study name and title	C0168Z03: A Multicenter, Open Registry of Patients with Psoriasis who are Candidates for Systemic Therapy Including Biologics (Psoriasis Longitudinal Assessment and Registry [PSOLAR])
Rationale and study objectives	To study the long-term safety of guselkumab.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab
Study design	Prospective, multicenter, longitudinal, observational safety study.
Study population	Adult patients with moderate to severe plaque psoriasis who receive guselkumab treatment and a comparator cohort of patients receiving IL-17 inhibitor treatments within routine clinical practice.
Milestones	Protocol submission: March 2018 Registry start: 20 June 2007 First patient in was 20 June 2007, which is prior to the protocol submission date because this registry was initially a REMICADE registry. The registry was expanded to include TREMFYA patients on 26 March 2018; the first TREMFYA patient was enrolled in PSOLAR on 25 February 2019. Interim report: 4Q 2025

	End of data collection for TREMFYA: 4Q 2029 Final report: 4Q 2030
Study name and title	CNTO1959PSO4001: Long-Term Benefits and Safety of Systemic Psoriasis Therapy: German Registry on the Treatment of Psoriasis with Biologics and Systemic Therapeutics (**Pso**riasis **Be**obachtung **s**ystemischer **t**herapie [PsoBest])
Rationale and study objectives	To study the long-term safety of guselkumab.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab
Study design	Prospective, observational cohort study.
Study population	Patients with moderate to severe plaque psoriasis who initiate treatment with a specific conventional systemic or biologic drug for the first time. Patients are grouped into treatment cohorts defined by specific therapeutic products: a TREMFYA-treated cohort, a non-biologic-treated cohort, and a cohort of patients treated with other biologics.
Milestones	Protocol submission: March 2018 Registry start: January 2008 First patient in was in January 2008, which is prior to the protocol submission date because TREMFYA was not initially included in this registry. The registry was expanded to include TREMFYA patients; the first TREMFYA patient was enrolled in PsoBest in January 2018. Interim report: After enrollment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year) End of data collection for TREMFYA: To be determined Final report: 4Q 2030
Study name and title	PCSIMM001324: A Retrospective Cohort Study Using Health Administrative Claims Databases to Assess Adverse Pregnancy and Infant Outcomes in Women Who Were Exposed to Guselkumab Versus Other Biologic Therapies During Pregnancy
Rationale and study objectives	To monitor pregnancy outcomes in women exposed to TREMFYA during pregnancy and linked infant outcomes in infants up to 1 year of age.
Safety concerns addressed	• Exposure during pregnancy
Study design	Observational, retrospective cohort study.
Study population	Pregnant women who satisfy the inclusion/exclusion criteria related to age at pregnancy start; inpatient and outpatient claims for psoriasis, psoriatic arthritis, and UC; and factors unrelated to these indications that may impact pregnancy outcomes (eg, exposure to teratogens, history of substance abuse).
Milestones	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

Study name and title	Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001: 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
Rationale and study objectives	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.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Study design	Extension of randomized clinical trial (5 years of follow-up in total)
Study population	Adult patients with moderately to severely active UC who received guselkumab and completed the Week 44 safety and efficacy evaluations in the Phase 3 Maintenance Study and who, in the opinion in the investigator, may benefit from continued treatment with guselkumab.
Milestones	Protocol submission: April 2024 Start of data collection: 31 July 2020 End of data collection: 3Q 2027 Final report: 3Q 2028
Study name and title	Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001: A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease
Rationale and study objectives	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 48 assessments. Total duration of follow-up will be 5 years.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Study design	Extension of randomized clinical trials (5 years of follow-up in total)
Study population	Adult patients with moderately to severely active CD who completed the Week 48 safety and efficacy evaluations in GALAXI 1, GALAXI 2, or GALAXI 3, were on active treatment, and, in the opinion of the investigator, may benefit from continued treatment.
Milestones	Protocol submission: April 2024 Start of data collection: - GALAXI 1: 10 May 2018 - GALAXI 2: 08 January 2020 - GALAXI 3: 22 January 2020 End of data collection: 3Q 2027 Final reports: 3Q 2028

Study name and title	Long-term extension of Study CNTO1959UCO3004: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis
Rationale and study objectives	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.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Study design	Extension of randomized clinical trial (5 years of follow-up in total)
Study population	Adult patients with moderately to severely active UC who received guselkumab and completed the Week 24 safety and efficacy evaluations and who, in the opinion of the investigator, may benefit from continued treatment with guselkumab
Milestones	Protocol submission: 2Q 2025 Start of data collection: 13 September 2022 End of data collection: 4Q 2028 Final report: 4Q 2029
Study name and title	Long-term extension of Study CNTO1959CRD3004: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Crohn's Disease
Rationale and study objectives	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.
Safety concerns addressed	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Study design	Extension of randomized clinical trial (5 years of follow-up in total)
Study population	Adult patients with moderately to severely active CD who received guselkumab and completed the Week 24 safety and efficacy evaluations
Milestones	Protocol submission: January 2025 Start of data collection: 19 January 2022 End of data collection: 2Q 2028 Final report: 2Q 2029

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances Not applicable				
Category 3 – Required additional pharmacovigilance activities				
C0168Z03 (PSOLAR) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	20 June 2007: The registry was expanded to include TREMFYA patients on 26 March 2018 and the first TREMFYA patient was enrolled in PSOLAR on 25 February 2019.
			Interim report	4Q 2025
			End of data collection for TREMFYA	4Q 2029
			Final report	4Q 2030
CNTO1959PSO4001 (PsoBest) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	January 2008: The registry was expanded to include TREMFYA patients and the first TREMFYA patient was enrolled in PsoBest in January 2018.
			Interim report	After enrollment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year)
			End of data collection for TREMFYA	To be determined
			Final report	4Q 2030

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Ongoing	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes in infants up to 1 year of age	• Exposure during pregnancy	Protocol submission	August 2018
			Start of data collection	31 December 2022
			Interim report	4Q 2025
			End of data collection	30 June 2030
			Final report	2Q 2031
Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 44 assessments as part of the Maintenance Study. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection	31 July 2020
			End of data collection	3Q 2027
			Final report	3Q 2028
Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 48 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection GALAXI 1 GALAXI 2 GALAXI 3	 10 May 2018 08 January 2020 22 January 2020
			End of data collection	3Q 2027
			Final reports	3Q 2028

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-term extension of Study CNTO1959UCO3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment following the Week 24 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	2Q 2025
			Start of data collection	13 September 2022
			End of data collection	4Q 2028
			Final report	4Q 2029
Long-term extension of Study CNTO1959CRD3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment following the Week 24 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	January 2025
			Start of data collection	19 January 2022
			End of data collection	2Q 2028
			Final report	2Q 2029

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious infection	**Routine risk communication:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) PL Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special Warnings and Precautions for Use) provides recommendations regarding treatment initiation, when patients should seek medical advice, and management of serious infection. PL Section 2 (What you need to know before you use Tremfya) advises patients not to use TREMFYA if they have an active infection. PL Section 2 (What you need to know before you use Tremfya) advises patients to seek medical advice if they are being treated for an infection, if they have an infection that does not go away or that keeps coming back, if they have TB or have been in close contact with someone with TB, or if they have an infection or have symptoms of an infection. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Malignancy	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serum sickness	**Routine risk communication:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) PL Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special Warnings and Precautions for Use) advises that TREMFYA should be discontinued immediately and appropriate therapy initiated in the event of a hypersensitivity reaction. PL Section 2 (What you need to know before you use Tremfya) advises patients to seek medical attention if they notice any signs indicating a possible serious allergic reaction. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Major adverse cardiovascular events (MACE)	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Exposure during pregnancy	**Routine risk communication:** SmPC Section 4.6 (Fertility, Pregnancy and Lactation) Package Leaflet Section 2 (What you need to know before you use Tremfya) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 (Fertility, Pregnancy and Lactation) advises that it is preferable to avoid the use of TREMFYA in pregnancy as a precautionary measure and that women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment with TREMFYA. PL Section 2 (What you need to know before you use Tremfya) advises that TREMFYA should not be used in pregnancy, that women of childbearing potential should avoid becoming pregnant and use adequate contraception, and that patients should speak to their doctor if they are pregnant, think they may be pregnant, or are planning to have a baby. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Use in patients ≥65 years of age	**Routine risk communication:** SmPC Section 4.2 (Posology and Method of Administration) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Long-term safety of guselkumab	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of TREMFYA.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infection	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029
Malignancy	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serum sickness	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029
Major adverse cardiovascular events (MACE)	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Exposure during pregnancy	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, Pregnancy and Lactation) Package Leaflet Section 2 (What you need to know before you use Tremfya) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up of reported pregnancies **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Final report: 2Q 2031
Use in patients ≥65 years of age	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and Method of Administration) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030
Long-term safety of guselkumab	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for TREMFYA® (guselkumab)

This is a summary of the risk management plan (RMP) for TREMFYA. The RMP details important risks of TREMFYA, and how more information will be obtained about TREMFYA's risks and uncertainties (missing information).

TREMFYA's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how TREMFYA should be used.

This summary of the RMP for TREMFYA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TREMFYA's RMP.

I. The Medicine and What it is Used For

TREMFYA is authorized for use in adults for the treatment of moderate to severe plaque psoriasis, active psoriatic arthritis (PsA), ulcerative colitis, and Crohn's disease (see SmPC for the full indications). It contains guselkumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of TREMFYA's benefits can be found in TREMFYA's EPAR, including its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004271/human_med_002183.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of TREMFYA, together with measures to minimize such risks and the proposed clinical trials for learning more about TREMFYA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

Information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of TREMFYA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TREMFYA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TREMFYA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
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

II.B. Summary of Important Risks

Important Potential Risk: Serious Infection	
Evidence for linking the risk to the medicine	Nonclinical data in mice suggest that blockade of interleukin (IL)-23 may predispose patients to infection.
	Although serious infections were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of serious infection in patients treated with guselkumab.

Important Potential Risk: Serious Infection	
Risk factors and risk groups	Risk factors for the development of serious infection include clinically significant metabolic and endocrine disorders such as diabetes, obesity, thyroid disorders, cardiovascular (CV) disorders, and renal and hepatic disorders; advanced age; and the concomitant use of corticosteroids, other biologics (including tumor necrosis factor [TNF]α inhibitors), and other immunosuppressants. *TB* The most common risk factors for the development of tuberculosis (TB) include conditions that weaken the immune system (eg, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppressive drugs such as methotrexate (MTX), connective tissue disease, renal failure, diabetes, and pregnancy. Exposure to TB is also a risk factor for the development of TB and patients who were born or lived in countries considered by the World Health Organization to have a high TB burden (incidence: >300 TB cases/100,000 population/year) or who have traveled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (ie, prisons) may also put patients at higher risk of development of TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of TB or who had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 (Contraindications) • SmPC Section 4.4 (Special Warnings and Precautions for Use) • PL Section 2 (What you need to know before you use Tremfya) • PL Section 4 (Possible side effects) Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 • Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 • Long-term extension of Study CNTO1959UCO3004 • Long-term extension of Study CNTO1959CRD3004 See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	No increased risk for malignancy was observed following the conduct of a 5-week intravenous (subchronic) and a 24-week SC (chronic) study with a 3-month recovery of guselkumab in cynomolgus monkeys conducted by the Marketing Authorization Holder (MAH). Although there are no validated models for carcinogenicity evaluations in cynomolgus monkeys, neoplasia has been observed in this species following repeated administration of other immunosuppressive drugs indicated in the treatment of psoriasis. Most data in the published literature pertaining to models of IL-23 ablation suggest that blockade of IL-23 may actually reduce the risk of carcinogenesis. A limited number of studies in the literature present conflicting data supporting an increased risk of malignancy in mice deficient for IL-23 and p19 exposed to ultraviolet-B (UVB) radiation. Although malignancies have been reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of malignancy in patients treated with guselkumab.
Risk factors and risk groups	Among psoriasis patients, an increased risk of solid cancers appears to be related to alcohol use and cigarette smoking. Exposure to psoralen + ultraviolet-A (PUVA) radiation and immunosuppressants (including cyclosporin and possibly MTX) has been associated with squamous cell carcinoma in psoriasis patients. There does not appear to be an increased risk of malignancy among patients with psoriatic arthritis. Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are at an increased risk of developing gastrointestinal malignancies such as colorectal cancer and extraintestinal malignancies such as hepatobiliary cancers and melanoma. The risk of colorectal cancer in patients with UC appears to be related to extent of UC disease, presence of low-grade dysplasia, strictures, primary sclerosing cholangitis, and post inflammatory polyps. The risks of prostate cancer, uterine cervical cancer, and thyroid cancer are increased in patients with UC but not in patients with CD. Patients with CD are at an increased risk of developing hematologic and lung cancers. Cigarette smoking has been shown to have a protective effect against the development and severity of UC, while smokers with CD have a worse disease course. Alcohol consumption may contribute to increased concentration of proinflammatory mediators, leading to a worsening of IBD symptoms. General risk factors for malignancy include increasing age, lifestyle factors (such as alcohol and tobacco use and obesity), family history of cancer, and certain environmental exposures.
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.

Important Potential Risk: Malignancy	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 • Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 • Long-term extension of Study CNTO1959UCO3004 • Long-term extension of Study CNTO1959CRD3004 See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Serum Sickness	
Evidence for linking the risk to the medicine	Although an infrequent occurrence, serum sickness has been reported in the published literature in association with the use of other mAb therapies.
Risk factors and risk groups	Not known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 (Contraindications) • SmPC Section 4.4 (Special Warnings and Precautions for Use) • PL Section 2 (What you need to know before you use Tremfya) • PL Section 4 (Possible side effects) Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 • Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 • Long-term extension of Study CNTO1959UCO3004 • Long-term extension of Study CNTO1959CRD3004 See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Major Adverse Cardiovascular Events (MACE)	
Evidence for linking the risk to the medicine	Evidence for an increased background risk of CV disease (ie, heart attack, stroke, and death related to heart attack and stroke) in patients with psoriasis (including PsA) is cited in the published literature. There is conflicting evidence of an increased background risk of CV disease (ie, heart attack, stroke, and death related to heart attack and stroke) in patients with inflammatory bowel disease (including UC and CD) in the published literature. Although MACE were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of MACE in patients treated with guselkumab.
Risk factors and risk groups	The risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, advanced age, male sex, obesity, and family history. Patients with psoriasis have been shown to be at increased risk for CV events (ie, MACE, defined as CV death, nonfatal MI, or nonfatal stroke) compared with the general population. Literature suggests psoriasis may be an independent risk factor due to the high inflammatory burden of psoriatic disease. Additionally, at least some CV risk factors occur more frequently in the psoriasis population compared with the general population. Specifically, these CV risk factors include pre-existing MACE conditions; uncontrolled or poorly controlled concomitant diseases such as diabetes, hypertension, hyperlipidemia, and obesity; and patient characteristics such as smoking. Of these, the association between psoriasis and dyslipidemia is less clear, with some studies showing that patients with psoriasis have significant dyslipidemia while others do not show a correlation. Notably, patients with severe psoriasis are more likely to demonstrate CV risk factors such as obesity, diabetes, and hypertension compared with those with no or mild psoriasis. Patients with IBD have not been shown to be at increased risk for CV events (ie, MACE, defined as CV death, nonfatal myocardial infarction, or nonfatal stroke) compared with the general population and IBD is not considered an independent cardiovascular risk factor. However, both UC and CD have been shown to be independently associated with an increased risk of acute myocardial infarction and IBD may be an independent risk factor due to the high inflammatory burden of IBD. Additionally, CV risk factors vary considerably among the IBD population compared with the general population. Patients with IBD have lower rates of hypertension and lower lipid levels but elevated rates of diabetes when compared with the general population. C-reactive protein and fibrinogen have also been shown to be elevated in the IBD population.
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.

Important Potential Risk: Major Adverse Cardiovascular Events (MACE)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 • Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 • Long-term extension of Study CNTO1959UCO3004 • Long-term extension of Study CNTO1959CRD3004 See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Exposure During Pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 (Fertility, Pregnancy and Lactation) • Package Leaflet Section 2 (What you need to know before you use Tremfya) Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in Patients ≥65 Years of Age	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 (Posology and Method of Administration) Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term Safety of Guselkumab	
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • C0168Z03 (PSOLAR) • CNTO1959PSO4001 (PsoBest) • Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 • Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 • Long-term extension of Study CNTO1959UCO3004 • Long-term extension of Study CNTO1959CRD3004 See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no clinical trials that are conditions of the marketing authorization or specific obligation of TREMFYA.

II.C.2. Other Studies in Postauthorization Development Plan

Trial	Purpose of the Trial
C0168Z03 (PSOLAR)	To study the long-term safety of guselkumab To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab
CNTO1959PSO4001 (PsoBest)	To study the long-term safety of guselkumab To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab

Trial	Purpose of the Trial
PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study)	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes in infants up to 1 year of age. To address the safety concern of: • Exposure during pregnancy
Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001	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. To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 48 assessments. Total duration of follow-up will be 5 years. To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Long-term extension of Study CNTO1959UCO3004	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. To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab
Long-term extension of Study CNTO1959CRD3004	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. To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Questionnaires

Table of Contents

Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections

Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Topic of Interest Questionnaire (TOIQ) for Hypersensitivity and Anaphylactic Reaction

Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Events

Of note, the above targeted follow-up questionnaires are utilized in conjunction with standard case follow-up procedures to request relevant additional information (general patient and product details) as necessary to provide a complete description of the safety event.

Serious Infection

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Medical History and Concurrent Conditions

☐ Prior history of exposure to TB
Details:
☐ Prior history of exposure to Hepatitis B/C
Details:
Details of vaccination history:
☐ The patient was considered immunocompromised *(underlying diagnoses, immunosuppressive therapy etc.)*
Details:

Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. Adverse Event Details

☐ The infection was present prior to starting the product
☐ There were unusual features of the patient's presentation or clinical course
Details:

Type of infection (e.g., pneumonia, endocarditis, etc.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

Malignancy

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Relevant Medical/Family History *(Provide prior diagnoses and details for checked items below)*

☐ Previous malignancy (Provide specific diagnosis):
☐ Occupational/Exposure history:
☐ Excessive sun exposure (Describe):
☐ History of PUVA (Psoralen + Ultraviolet-A rays)
☐ History of radiation
Dose of radiation:
Area treated:
Age (or date of therapy) of the patient when they were treated with radiation:
Indication for radiation:
Any radiation induced changes?
☐ Pre-malignant lesions, e.g., Barret's oesophagus, Bowen's disease. Details:
Viral infections: ☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV
☐ Other relevant risk factors for malignancy (Excluding medications):
☐ Family history of malignancy (Provide specific diagnoses for each):
☐ In first degree relatives:
☐ In more distant relatives:

☐ Previous history of tumor necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):
Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)
Include drug indication, dose levels, and treatment duration (e.g., methotrexate, clophosphamide, vincristine, doxorubicine, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Date/Stop Date (dd-MMM-yyyy)

☐ Cytogenetic abnormalities detected at any point in time? *(*Include those relevant for any malignancy including myeloma – this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc., or cytogenetic abnormalities relevant to myeloma)

MCN:

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, metastases, lymph node involvement and staging system used:

Additional diagnostic information, including finding that support specified staging; specialty consultations (Attach reports, if available): Final diagnosis:

☐ **Lymphoma**

☐ Non-Hodgkin's lymphoma

Histologic subtype: Immunophenotype: Cytogenetics:

☐ Hodgkin's lymphoma

Histologic subtype:

Was the lymphoma tissue tested for Epstein-Barr virus (EBV) (e.g., by in situ hybridization and/or immunohistology analysis)? ☐ No ☐ Yes (Attach report)

If Yes, Test Result: ☐ EBV positive ☐ EBV negative

☐ **Second malignancy** (A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) (List):

☐ **Secondary malignancy** (A cancer caused by treatment for a previous malignancy e.g., Treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) (*List*):

(Ref.http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf)

Malignancy screening/Preventive measures (Include those that are relevant to the specific malignancy that is being reported, e.g., recent mammography, breast exam, Pap smear, sigmoidoscopy or colonoscopy, faecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine etc.)

Screening Test/Preventive Measure	Date (dd-MMM-yyyy)	Results (Including units and reference ranges where applicable)

3. Treatment

What was the response to the first treatment for malignancy?

☐ Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease

Serum Sickness

Topic of Interest Questionnaire (TOIQ) for Hypersensitivity and Anaphylactic Reaction

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

1. Product Details

Did the patient have a prior hypersensitivity reaction to any vaccine, drug, or food?

Product	Drug	Vaccine	Food
Name of the product:			
Date [dd-MMM-yyyy]:			
Time:	☐ AM ☐ PM	☐ AM ☐ PM	☐ AM ☐ PM

How many doses of the product did the subject receive prior to the hypersensitivity event?

Product	Drug	Vaccine	Food
Number of doses			

When was the patient last exposed to product causing hypersensitivity reaction?

Product	Drug	Vaccine	Food
Date [dd-MMM-yyyy]			

☐ Was the patient pre-medicated prior to receiving the product?
List the pre-medication regimen:

☐ Did the patient take any new product (prescribed or OTC) or food prior to the hypersensitivity reactions? List additional details including product name, date/time of exposure:

☐ Has the patient been exposed to any toxic materials, fumes, pollution? Provide details including product name, date/time of exposure:

☐ Has the patient been treated with immunomodulating or immunosuppressing medications or received any other vaccine around the time of the COVID-19 vaccination?

2. Relevant Medical History Details

Does the patient have any of the following? (check if applicable)

☐ Drug intolerance/allergic reactions/hypersensitivity reactions
To which product/vaccine/substance/food/cosmetics/aeroallergens/insect venom:

☐ Anaphylaxis
To which product/vaccine/substance/food/cosmetics/aeroallergens/insect venom:

☐ Asthma: Duration/severity:

☐ Allergic rhinitis (Hay fever) Duration:

☐ Atopic dermatitis: Duration/severity:

☐ Urticaria (Hives): Duration/severity:

☐ Inherited/acquired complement abnormalities (Specify):

☐ Other pertinent medical history or concurrent conditions (Specify):

MCN:

3. Event Details:

Time from the dosing of the product/vaccine to onset of symptoms (TTO):

☐ minutes ☐ hours ☐ days (Check one)

Duration of the event:

Clinical Signs and Symptoms:

☐ Red and itchy eyes	☐ Generalized urticaria (hives) or generalized erythema
☐ Generalized prickle sensation	☐ Angioedema, localized or generalized
☐ Localized injection site urticaria	☐ Generalized pruritus with skin rash
☐ Tachycardia	☐ Measured hypotension
☐ Capillary refill time >3 s (without hypotension)	☐ Capillary refill time >3 s (with hypotension)
☐ Decreased level of consciousness	☐ Reduced central pulse volume
☐ Persistent dry cough	☐ Loss of consciousness
☐ Hoarse voice	☐ Bilateral wheeze (bronchospasm)
☐ Difficulty breathing without wheeze or stridor	☐ Stridor
☐ Sensation of throat closure	☐ Upper airway swelling (lip, tongue, throat, uvula or larynx)
☐ Sneezing, rhinorrhea	☐ Respiratory distress
☐ Diarrhea	☐ Tachypnea
☐ Abdominal pain	☐ Increased use of accessory muscles
☐ Nausea	☐ Cyanosis
☐ Vomiting	☐ Recession
☐ Feeling hot	☐ Flushing
☐ Other; Specify:	☐ Grunting

Skin manifestation:

Describe in detail and provide a photo, if available (*Erythema, macular, papular, morbilliform, urticaria/angioedema, exfoliative dermatitis/erythroderma, bullous dermatitis, blistering, photoallergic reaction*):

MCN:

Generalized	☐ No	☐ Yes (Describe):			
Localized	☐ No	☐ Yes (Describe):			
Grade	☐ 1	☐ 2	☐ 3	☐ 4	
Approximate % of Body Surface Area Involvement			< 10 % ☐	10-30 % ☐	>30 % ☐
Mucus membranes:		☐ No	☐ Yes (Specify):		
Skin necrosis:		☐ No	☐ Yes (Specify):		
Was the patient seen by a dermatologist?		☐ No	☐ Yes (Specify and provide the report, if available):		
Was a skin biopsy performed?		☐ No	☐ Yes (Provide report, if available)		
Other:					

4. Diagnosis of the reported event:

☐ Hypersensitivity reaction

☐ Anaphylactic reaction

☐ Anaphylactoid reaction

☐ Anaphylactic shock

☐ Other; (Specify):

5. Laboratory findings *(Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available.)*

Laboratory test or Diagnostic Studies	**Date Performed** (dd-Mmm-yyyy)	**Results with units, if applicable**	**Reference Ranges, if applicable** (or state if abnormal or elevated/ reduced)
☐ Mast cell tryptase elevation			
☐ IgE			
☐ Complement			
☐ Pathology findings			
☐ Other relevant tests (Specify):			

6. Treatment *(Specify medications, response, and need for ER evaluation/hospitalization)*

Was the patient treated? (if Yes, specify below)

☐ Adrenalin	☐ Steroids (Oral)	☐ Antihistamines (Oral)	☐ IV fluids (Specify):
☐ Oxygen	☐ Steroids (IV)	☐ Antihistamines (IV)	☐ Bronchodilators (Specify):
☐ CPR	☐ Other (Specify):		

Thank you for completing this form.

Major Adverse Cardiovascular Events (MACE)

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Cardiovascular Events

Manufacturer Control Number: Drug generic (TRADE) Name:
Date of Report: [dd-MMM-yyyy]

1. **Drug Details:**

   Number of doses (e.g., injections, infusions) given prior to cardiovascular event:
   Recent **dose change? Details:**
   When did the patient **last** receive the product **before the current dose?**
   Date: [dd-MMM-yyyy], Time:
   Date and time of dose (e.g., injections, infusions) **after which this** cardiovascular event occurred:
   [dd-MMM-yyyy], Time:
   Date and time of onset of cardiovascular event **reported now:** [dd-MMM-yyyy], Time:

2. **Relevant medical history** *(Provide prior diagnoses relevant laboratory data [including echo and ischemic evaluation], dates, etc. below.)*

   ☐ Hypertension
   ☐ Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia
   ☐ Obesity
   ☐ Coronary artery disease
   ☐ Myocardial infarction
   ☐ Valvular heart disease
   ☐ History of percutaneous coronary intervention
   ☐ Coronary artery bypass graft
   ☐ Congenital heart disease
   ☐ Arrhythmias
   ☐ Cardiomyopathy
   ☐ Pericarditis
   ☐ Congestive heart failure
   ☐ Peripheral artery disease
   ☐ Diabetes mellitus
   ☐ Renal impairment
   ☐ Liver disease
   ☐ Headaches
   ☐ Head trauma
   ☐ Transient ischemic attack
   ☐ Ischemic cerebrovascular accident
   ☐ Hemorrhagic cerebrovascular accident
   ☐ Other (Specify):

   Relevant family history:
   ☐ Coronary disease ☐ Stroke
   ☐ Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia
   ☐ Myocardial infarction
   ☐ Diabetes mellitus
   ☐ Family history of long QT syndrome
   ☐ Other (Specify):

MCN:

3. Adverse Event: Patient's symptoms/Signs *(Check all that apply and provide details below.)*

☐ Dizziness	☐ Exercise intolerance	☐ Chest discomfort
☐ Palpitations	☐ Dyspnea	☐ Hemoptysis
☐ Edema	☐ Cough	☐ General malaise
☐ Syncope	☐ Sudden death	☐ Aphasia
☐ Visual disturbance	☐ Transient weakness (i.e., slurred speech)	
☐ Sensory changes	☐ Sweating	☐ Nausea/vomiting
☐ Jaw pain	☐ Left arm pain	☐ Ataxia
☐ Facial weakness	☐ Extremity paralysis	☐ Altered gait
☐ Other relevant details:		

Annex 6: Details of Additional Risk Minimization Activities

Not applicable.