Unit: Technical Assessment Unit

Public assessment report for biological products

Tremfya

Administrative information:

Trade name of the medicinal product:	- Tremfya concentrate for solution for I.V infusion. - Tremfya concentrate for solution in prefilled pen.
INN (or common name) of the active substance(s):	Guselkumab 200 mg /20.0 ml(10mg/ml) Guselkumab 200 mg in 2 mL solution (PFP).
Manufacturer of the finished product	Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen - Switzerland.
Marketing Authorization holder	Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse - Belgium.
Applied Indication(s):	- Treatment of adult patients with moderately to severely **active ulcerative colitis** who have an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment. - 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.
Pharmaceutical form(s) and strength(s):	- Concentrate for solution for I.V infusion, Guselkumab 200 mg /20.0 ml(10mg/ml). - Solution for subcutaneous injection in pre-filled pen, Each pre-filled pen contains: Guselkumab 200 mg in 2 mL solution.

(Tremfya 200mg Vial/PFP)

Route of administration	S.C and I.V
Approved Pack	Tremfya 200 mg concentrate solution for infusion vial: 200 mg concentrate solution for infusion in a type I clear glass vial closed with a butyl rubber stopper, an aluminium seal and polypropylene flip top Tremfya 200 mg solution for injection in pre-filled pen: 2 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper, assembled in a pre-filled pen with an automatic needle guard.
Registration track	Reliance Level 1
Type of registration (EMA/FDA – Local)	EMA approved

List of abbreviations:

ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AUC	area under the plasma concentration curve
CD	Crohn's disease
CDC	Complement-Dependent Cytotoxicity
CHO	Chinese hamster ovary
Cmax	maximum plasma concentration
CNS	central nervous system
CNTO 1959	Guselkumab
CRP	C-reactive protein
EFD	Embryo-Fetal Development
ePPND	Enhanced Pre- and Postnatal Development
G-CSF	Granulocyte Colony-Stimulating Factor

hIL	human interleukin
IgG1λ	Immunoglobulin G1 lambda
IL	interleukin
IV	Intravenous
LTE	long-term extension
mAb	monoclonal antibody
NOAEL	no observed-adverse-effect-level
PK	Pharmacokinetics
SAEs	serious adverse events
SC	Subcutaneous
$t_{1/2}$	elimination half-life
TDAR	T-cell dependent antibody response
TEAEs	treatment-emergent adverse events
TNFα	Tumor necrosis factor alpha
UC	ulcerative colitis

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Dossier initial submission and evaluation process:

-The file evaluated according to EDA regulation based on reliance pathway (Reliance level 2), the company submitted Complete CTD file.

1. Introduction

Guselkumab is a fully human IgG1λ monoclonal antibody against IL-23. It neutralises the biological activities of the cytokine. The guselkumab active substance (AS) is manufactured by Biogen, Inc., Research Triangle Park, in North Carolina, USA, and Janssen Biologics (Ireland) in Cork, Ireland. There is no change to the active substance section. The approved guselkumab formulated active substance for the 100 mg PFS FP presentations is also used for manufacturing of the new proposed 200 mg presentations (FVP and PFS FP).

1. **Quality aspects:**

- **Manufacturer of Drug Substance:**

- The Finished product is manufactured at Barnahely, Ringaskiddy Co. Cork, Ireland.

Manufacturing of DS is performed in accordance with cGMP regulations.

- **Manufacturer of Drug product:**

- The Finished product is manufactured at Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen - Switzerland.

-Manufacturing of DP is performed in accordance with cGMP regulations.

- **Stability**

Drug substance:

- Approved Storage Conditions of the active substance: Store at (-40°C)

-Approved shelf life for the active substance:36 months

Drug product:

-Approved Storage Conditions of the finished product:

Finished product:

- Store at 2-8°C. (Don't Freeze)
- Keep the container in the outer carton in order to protect from light.

-Approved shelf life for the finished product: 24 months

1. **Non–clinical aspect**

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) directed against the p19 subunit of interleukin (IL)-23.
Guselkumab is produced in a fed-batch cell culture process using a manufacturing cell line (C1707B) that was developed from a genetically engineered Chinese hamster ovary (CHO) cell line.
Guselkumab binds to the p19 protein subunit of extracellular human IL-23 with high specificity and affinity. By binding to the p19 subunit of IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-mediated intracellular signaling, activation and cytokine production.

Pharmacology:
- A thorough preclinical In vitro study program has been conducted. Primary pharmacodynamic studies characterized guselkumab in terms of its binding interactions, mechanism of action, functional effects of neutralization, and species cross-reactivity. The non-clinical studies adequately provide evidence that guselkumab neutralizes human IL-23 with high affinity and specificity and consequently inhibits the immune response by Th17 lymphocytes. There is no evidence that Fc-mediated effector functions such as ADCC or CDC contribute to the mechanism of action of guselkumab.
- CNTO1959 is a fully human IgG1λ monoclonal antibody that selectively binds to the p19 subunit of IL-23 and neutralizes human IL-23. CNTO1959 does not bind to or neutralize mouse IL-23. Therefore, the in vivo activity of CNTO1959 in mouse models of human disease could not be assessed. Instead, the effect of CNTO1959 on inflammatory responses induced by in vivo administration of human IL-23 was explored.
- Guselkumab administration was shown to attenuate rhIL23-induced increases in serum levels of cytokines IL-1α and G-CSF without any significant change in TNFα or G-CSF levels. The low number of study animals and the high deviations of the data prevent drawing a robust conclusion. It was not possible to measure IL-17A production induced by hIL-23, impairing the interpretation of the data. Thus, this animal model of testing the effectiveness of hIL-23 and, consequently, the inhibitory capability of guselkumab is of limited value.
- Secondary pharmacological in vitro studies investigated the tissue cross-reactivity of guselkumab. Guselkumab was not found to bind to pig cardiac myosin, pig muscle myosin or recombinant human myosin.
- In vivo secondary pharmacodynamic and pharmacodynamic interactions studies have not been conducted. This approach is acceptable as guselkumab is highly specific and no other binding targets are expected. Similarly, no other specific IL-23 antagonists, except gustekinumab are known, therefore it is unlikely to have pharmacodynamic interactions with co-administered drugs.

(Tremfya 200mg Vial/PFP)

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

Pharmacokinetics:
- Systemic exposure (Cmax and AUC) of guselkumab increased in an approximately dose-proportional manner following the administration of IV or SC doses of guselkumab in guinea pigs and cynomolgus monkeys.
- Mean terminal $T_{1/2}$ values following a single SC or IV administration in cynomolgus monkeys were similar, indicating that the elimination process is independent of the route of administration.
- Based on Vs values obtained from single-dose IV studies in cynomolgus monkeys, the volume of distribution of guselkumab is similar to that of most IgG-based therapeutic mAbs.

Toxicology:
- Guselkumab was well tolerated in cynomolgus monkeys and had no adverse effects on any parameter evaluated at the highest doses and longest durations tested. The NOAEL was determined to be 50 mg/kg/week SC.
- The AUC_{inf} and Cmax obtained from the 24 weeks repeated dose toxicity were more than 50 and 200 folds higher compared to clinical Cmax and AUC_{inf} levels (single SC dose of 100 mg/kg).
- Moderate drug accumulation in systemic circulation occurred when guselkumab was administered as repeated SC doses to guinea pigs and as repeated IV or SC doses to cynomolgus monkeys. There were no apparent sex-related differences in PK parameters in monkeys after weekly IV (50 mg/kg) or SC (10 or 50 mg/kg) administration for 5 weeks, and after weekly SC administration for 24 weeks.
- Following repeated SC administration to pregnant animals, guselkumab was distributed across the placenta into the developing fetus of both guinea pigs and cynomolgus monkeys. Guselkumab does not appear to be excreted into the breast milk of cynomolgus monkeys, as samples obtained from maternal animals on PPD 28 were below the lowest quantifiable concentration for the assay.
- In the absence of standard carcinogenicity testing in rodents, a weight of evidence approach was utilized to determine the potential for carcinogenicity following long-term antagonism of IL-23. This includes evidence from the toxicity studies conducted in monkeys and clinical studies in humans that indicate no increased level of concern for malignancy. However, although the risk for malignancy associated with long-term inhibition of IL-23 following administration of guselkumab to humans is considered to be low, it cannot be ruled out as a potential hazard associated with modulation of IL-23 activity.
- Guselkumab had no effects in pregnant cynomolgus monkeys or their infants following SC doses up to 50 mg/kg/week in an ePPND study. Fertility and early EFD were unaffected in the male and female guinea pig following twice-weekly SC administration of up to 100 mg/kg guselkumab.

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- Guselkumab was immunogenic in both guinea pigs and monkeys. ADA were detected in 2 (2.2%) of 90 monkeys administered weekly IV or SC doses of guselkumab; these ADA-positive animals exhibited an accelerated decline in serum guselkumab concentrations. One (4.2%) of 24 infants from the ePPND study was found to be ADA positive. A higher incidence of ADA was seen after SC doses of guselkumab were administered twice weekly in guinea pigs: 55 (83.3%) of 66 pregnant and non-pregnant female guinea pigs were ADA-positive, and 23 (24.7%) of 93 male guinea pigs were ADA-positive. ADA-positive infants were also identified, as 6 of 32 (19%) pooled fetal samples from guselkumab-treated pregnant females were ADA-positive.
- Plasma membrane binding of guselkumab in the cynomolgus monkey and human tissue in in vitro TCR studies was limited to macrophages and/or dendritic cells.
- A potential effect of immunosuppression includes infections. During the conduct of the nonclinical toxicology program, no guselkumab-related infections were noted in animals treated with IV or SC doses up to 50 mg/kg. Moreover, TDAR, as a measure of immune competence, was unaltered during the conduct of the 5-week/24-week study, or during the ePPND study in adults or infants. No adverse guselkumab-related clinical observations, hematology or lymphoid histopathology changes were noted.

Overall conclusion: Guselkumab is acceptable from the pre-clinical point of view.

2. Clinical aspect:

Clinical Overview

Guselkumab is a fully human monoclonal antibody that selectively inhibits interleukin-23 (IL-23), a key cytokine involved in chronic intestinal inflammation. Its mechanism of action supports targeted modulation of immune pathways implicated in inflammatory bowel diseases.
The clinical development program for guselkumab cover **ulcerative colitis (UC)** and **Crohn's disease (CD)**, The program evaluated intravenous and subcutaneous induction regimens, multiple maintenance dosing strategies, pharmacokinetics, immunogenicity, and long-term safety.

Ulcerative Colitis

The clinical development program in ulcerative colitis evaluated guselkumab in adult patients with moderately to severely active UC who had failed or were intolerant to conventional treatments and/or advanced therapies, including TNF-α antagonists, vedolizumab, or tofacitinib.

The program consisted of:

- **Two Phase 3 controlled studies**:
  - One intravenous (IV) induction study
  - One randomized withdrawal subcutaneous (SC) maintenance study
- **One supportive Phase 2b IV dose-ranging induction study**

All UC studies were conducted under a single master protocol (**QUASAR; CNTO1959UCO3001**), ensuring consistency in study design, endpoints, and patient populations.

Collectively, these studies provide **at least one year of treatment experience** (≥56 weeks), including IV induction followed by SC maintenance therapy. Participants completing the maintenance phase who were considered to benefit from continued treatment were eligible to enter a **long-term extension (LTE)**, providing up to **four additional years of follow-up** to further evaluate long-term efficacy and safety.

Summary of UC Clinical Studies

- Phase 2a supportive study
- Phase 2b/3 supportive induction study
- Phase 2b/3 pivotal induction study
- Phase 2b/3 pivotal maintenance study

Crohn's Disease

The clinical development program for Crohn's disease evaluated guselkumab in adults with moderately to severely active CD who had an inadequate response, lost response, or were intolerant to conventional therapies and/or advanced therapies, including TNF-α inhibitors, vedolizumab, or tofacitinib. In the GALAXI and GRAVITI studies, BIO-failed patient populations had prior failure or intolerance to TNF-α inhibitors and/or vedolizumab only.

The program comprised two complementary development pathways:

- The **GALAXI Phase 2/3 program**, supporting IV induction followed by SC maintenance therapy
- The **GRAVITI Phase 3 study**, supporting SC induction followed by SC maintenance therapy

The GALAXI program was conducted under a single master protocol (**CNTO1959CRD3001**) and included:

- One Phase 2 dose-ranging study (GALAXI 1)
- Two identically designed Phase 3 confirmatory studies (GALAXI 2 and GALAXI 3)

Dose selection for Phase 3 was based on the totality of efficacy, safety, and pharmacokinetic data from the Phase 2 study. All GALAXI studies employed a treat-through design, allowing continuous treatment regardless of induction response, with predefined crossover options for placebo non-responders.

The **GRAVITI Phase 3 study (CNTO1959CRD3004)** evaluated a fully subcutaneous induction regimen followed by alternative SC maintenance dosing schedules. Participants completing the induction and maintenance phases were eligible for long-term extension periods to further assess durability of response and long-term safety.

Summary of CD Clinical Studies

- Phase 2 dose-ranging study
- Phase 2/3 pivotal confirmatory studies
- Phase 3 pivotal SC induction and maintenance study

- **Clinical Efficacy (Including Immunogenicity)**

Ulcerative Colitis

The QUASAR clinical program demonstrated that guselkumab is **effective during both induction and maintenance phases** in adults with moderately to severely active UC.
Induction treatment with **guselkumab 200 mg IV at Weeks 0, 4, and 8** resulted in clinically meaningful improvements in disease activity. Maintenance treatment with **100 mg SC every 8 weeks** sustained clinical benefit through long-term follow-up. An alternative maintenance regimen of **200 mg SC every 4 weeks** provided additional benefit for patients with an inadequate response to induction therapy.
A slight decline in efficacy was observed through Week 44; however, responses remained clinically relevant, and longer-term data are being generated to further characterize durability of effect.
Pharmacokinetic analyses demonstrated a **positive exposure response relationship**, with higher serum guselkumab concentrations associated with improved efficacy outcomes. Reductions in inflammatory biomarkers, including **C-reactive protein (CRP)** and **fecal calprotectin**, were observed at higher drug concentrations.

Crohn's Disease

In Crohn's disease, guselkumab induction and maintenance treatment was effective in patients with moderately to severely active disease. Both **200 mg IV** and **400 mg SC induction regimens** administered at Weeks 0, 4, and 8 resulted in clinically meaningful improvements. Maintenance treatment with **100 mg SC every 8 weeks** provided sustained efficacy, with an alternative **200 mg SC every 4 weeks** regimen available for patients with insufficient response.

Immunogenicity

Across UC and CD studies, guselkumab demonstrated **low immunogenicity**. The incidence of anti-guselkumab antibodies was low and **did not have a clinically meaningful impact** on pharmacokinetics, efficacy, or safety outcomes. Immunogenicity findings were consistent with previous experience in psoriasis and psoriatic arthritis.

- **Clinical Safety**

Ulcerative Colitis

Safety data from induction and maintenance phases indicate that guselkumab is **generally well tolerated**. The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) was **comparable to or lower than placebo** during induction. Most adverse events were mild to moderate in severity.

Long-term safety through maintenance was consistent with the **established safety profile** of guselkumab in other approved indications. Serious infections, malignancies, hepatic disorders, and events leading to treatment discontinuation were infrequent, with no new safety signals identified.

Crohn's Disease

In Crohn's disease studies (GALAXI and GRAVITI), rates of SAEs were lower in guselkumab-treated groups compared with placebo during induction. Serious adverse events were primarily gastrointestinal and reflective of underlying disease activity.

Malignancies and serious infections were rare and assessed as **unrelated to study treatment**. A single case of tuberculosis was reported, consistent with background risk in this patient population.

Hepatic events were infrequent and comparable to placebo.

Overall, guselkumab's safety profile in CD was **consistent with that observed in UC** and with its established profile in psoriasis and psoriatic arthritis.

- **Benefit-Risk Conclusion**

The clinical development program demonstrates that guselkumab provides **clinically meaningful and durable efficacy** in patients with moderately to severely active ulcerative colitis and Crohn's disease, including those with prior inadequate response or intolerance to biologic therapies.

These benefits are supported by a **well-characterized and acceptable safety profile**, low immunogenicity, and sustained biomarker improvement. No new or unexpected safety concerns were identified during induction or long-term maintenance treatment.

Based on the totality of evidence, guselkumab demonstrates a **favorable benefit-risk balance** in both ulcerative colitis and Crohn's disease.

- **Overall Conclusion**

Guselkumab represents an effective treatment option for adults with moderately to severely active ulcerative colitis and Crohn's disease. The clinical program confirms its ability to induce and maintain disease control, with flexible dosing options to address individual patient needs.

The consistency of efficacy, low immunogenicity, and established safety profile support guselkumab as a **valuable therapeutic option** in the management of inflammatory bowel disease.

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https://www.ema.europa.eu/en/documents/assessment-report/tremfya-epar-public-assessment-report_en.pdf