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 (UC)

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Induction Study 1 (Phase 2b Induction Dose-ranging Study)ObjectivesPrimary ObjectivesThe primary objectives of this study are, in participants with moderately to severely active UC:* To evaluate the efficacy of guselkumab as induction therapy.* To...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON54924

Source
ToetsingOnline

Brief title
QUASAR

Condition

- Gastrointestinal inflammatory conditions

Synonym
Chronic inflammation of the intestinal wall, Inflammatory Bowel Disease

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen CILAG B.V.

Intervention

Keyword: Dose Ranging, Guselkumab, Maintenance, Ulcerative Colitis

Outcome measures

Primary outcome

Induction study 1 & 2:

The primary endpoint in this study is clinical response at Induction Week 12

(Week I-12).

Maintenance Study:

The primary endpoint in this study is clinical remission at Maintenance Week 44

(Week M-44).

Secondary outcome

Induction study 1:

* Clinical remission at Week I-12.

* Symptomatic remission at Week I-12.

* Endoscopic healing at Week I-12.

* Histo-endoscopic healing at Week I-12.

Induction Study 2:

* Symptomatic remission at Week I-12.

* Endoscopic healing at Week I-12.

* Clinical response at Week I-12.

* Histo-endoscopic healing at Week I-12.

* Symptomatic remission at Week I-4.

Maintenance Study:

* Symptomatic remission at Week M-52.

* Endoscopic healing at Week M-52.

* Corticosteroid-free (ie, not requiring any treatment with corticosteroids for

at least 8 weeks prior) clinical remission at Week M-52.

* Clinical response at Week M-52.

* Histo-endoscopic healing at Week M-52.

* Clinical remission at Week M-52 among the participants who had achieved

clinical remission at maintenance baseline.

Study description

Background summary

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

The Phase 2b/3 clinical development program for guselkumab in ulcerative colitis (UC) is designed to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active UC. Under this single protocol

(CNTO1959UCO3001), there are 3 separate studies:
* Induction Study 1 (Phase 2b Induction Dose-ranging Study)
* Induction Study 2 (Phase 3 Induction Study)
* Maintenance Study (Phase 3 Maintenance Study)
Participants who complete the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the long-term extension (LTE) of the Maintenance Study and receive up to another 2 years of treatment.

Study objective

Induction Study 1 (Phase 2b Induction Dose-ranging Study)
Objectives
Primary Objectives
The primary objectives of this study are, in participants with moderately to severely active UC:
* To evaluate the efficacy of guselkumab as induction therapy.
* To evaluate the safety of guselkumab as induction therapy.
* To evaluate the dose-response of guselkumab to inform induction dose selection for the Phase 3 induction study.
Secondary Objectives
The secondary objectives of this study are, in participants with moderately to severely active UC:
* To evaluate the impact of guselkumab on health-related quality of life (HRQoL) and health economics outcome measures.
* To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab therapy, including changes in C-reactive protein (CRP) and fecal calprotectin.

Induction Study 2 (Phase 3 Induction Study)
Objectives
Primary Objectives
The primary objectives of this study are, in participants with moderately to severely active UC:
* To evaluate the efficacy of guselkumab as induction therapy.
* To evaluate the safety of guselkumab as induction therapy.
Secondary Objectives
The secondary objectives of this study are, in participants with moderately to severely active UC:
* To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
* To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

Maintenance Study (Phase 3 Maintenance Study)
Objectives
Primary Objectives

The primary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:
* To evaluate the efficacy of maintenance regimens of guselkumab.
* To evaluate the safety of maintenance regimens of guselkumab.
Secondary Objectives
The secondary objectives of this study are, in participants with moderately to severely active UC who were induced into clinical response with guselkumab:
* To evaluate the impact of guselkumab on HRQoL and health economics outcome measures.
* To evaluate the PK, immunogenicity, and PD of guselkumab therapy, including changes in CRP and fecal calprotectin.

Study design

All 3 studies (Induction Study 1, Induction Study 2, Maintenance Study) under this single protocol will be randomized, double-blind, placebo-controlled, parallel-group, multicenter studies to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active UC. The induction studies (Induction Study 1 and Induction Study 2) will target participants 18 years of age or older with moderately to severely active UC who have demonstrated an inadequate response or failure to tolerate conventional (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids) or advanced therapy (ADT; ie, tumor necrosis factor alpha [TNF*] antagonists, vedolizumab, or tofacitinib). Participants who had an inadequate response or failure to tolerate advanced therapy (ADT-Failure) will comprise a minimum of approximately 40% and a maximum of approximately 50% of the population for the following: 1) the first 200 participants randomized in Induction Study 1 for the interim analysis and induction dose decision; and 2) the total population of Induction Study 2. The Maintenance Study is a randomized withdrawal study targeting participants with moderately to severely active UC who have demonstrated a clinical response to guselkumab treatment in either Induction Study 1 or Induction Study 2.
Overall, the program will evaluate guselkumab treatment through at least 64 weeks of induction and maintenance therapy. Participants who complete the safety and efficacy evaluations at Week M-52 of the Maintenance Study and who may benefit from continued study intervention, in the opinion of the investigator, will have the opportunity to participate in the LTE of the Maintenance Study for up to an additional 2 years of treatment (ie, Week M-52 to Week M 168) to evaluate the efficacy and safety of long-term maintenance treatment.
All UC-specific medical therapies (ie, oral 5-aminosalicylic (5-ASA) compounds, oral corticosteroids, 6 MP, AZA, or methotrexate [MTX]) must be maintained at a stable dose through to the end of the induction studies and can only be discontinued or reduced in dose if investigator judgment requires it because of toxicity or medical necessity. The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during Induction Study 1 or Induction Study 2 will prohibit a participant from

entering the Maintenance Study.
For participants who are receiving oral corticosteroids on entry in the Maintenance Study, the investigator must begin tapering the daily dose of corticosteroids at Week M-0. Other UC-specific medical therapies (ie, oral 5-ASA compounds, 6-MP, AZA, or MTX) must be maintained at stable doses through Week M 52 unless investigator judgment requires that the therapy be discontinued, or the dose reduced because of toxicity or medical necessity. Tapering of the daily dose of corticosteroids may be paused for participants meeting clinical flare criteria. Participants meeting criteria for loss of clinical response during the Maintenance Study will be eligible for a single blinded dose adjustment as described in the protocol.
During Induction Study 1, an interim analysis of the first 200 randomized participants who have completed the Week I-12 visit or have terminated study participation prior to Week I-12 will be performed. The purpose of this interim analysis is to select a single induction dose for confirmatory evaluation in the Phase 3 induction study (Induction Study 2). A Dose Selection Committee, composed of sponsor management representatives from Clinical, Safety, Biostatistics, and Clinical Pharmacology, who are not associated with study conduct, will be responsible for selecting the induction dose of guselkumab to be evaluated in Induction Study 2. While the data from the first 200 randomized participants is being evaluated, participants will continue to be enrolled in Induction Study 1, up to a maximum of 440 participants. Once the induction dose selection has occurred, participants will begin randomization into Induction Study 2.
Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed at time points indicated in the appropriate Schedule of Activities (SoA).
An external, independent Data Monitoring Committee (DMC), with defined roles and responsibilities as governed by a DMC charter, will assess the safety of participants across the 3 studies.

Intervention

At Weeks I-12 and/or I-24 of Induction Study 1 and Induction Study 2, participants will be evaluated for clinical response. Eligibility for the Maintenance Study will be determined by the participant's clinical response status.
*
Induction Study 1 (Phase 2b Induction Dose-ranging Study)
From Week I-0 Through Week I-12
In Induction Study 1, participants will be randomized to 1 of 4 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I 12..
* Guselkumab 400 mg IV: Participants will receive guselkumab 400 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
* Guselkumab 200 mg IV: Participants will receive guselkumab 200 mg IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
* Placebo: Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie,

3 IV doses).
From Week I-12 Through Week I-24
Guselkumab
For participants who received 3 IV guselkumab doses (400 mg or 200 mg), subsequent study intervention will be based on clinical response status at Week I-12 as follows:
* Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be re-randomized to either receive guselkumab 200 mg subcutaneously (SC) every 4 weeks (q4w), guselkumab 100 mg SC every 8 weeks (q8w), or placebo.
* Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I 12, I 16, and I-20 to maintain the blind.
At Week I-24, subsequent study intervention will be based on clinical response status as follows:
* Guselkumab clinical responders at Week I-24 (ie, delayed responders to guselkumab): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
* Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.
Placebo
For participants who received 3 IV placebo doses, subsequent study intervention will be based on clinical response status at Week I-12 as follows:
* Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
* Placebo clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg IV at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.
At Week I-24, subsequent study intervention will be based on clinical response status as follows:
* Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
* Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Induction Study 2 (Phase 3 Induction Study)
In Induction Study 2, participants will be randomized to 1 of 2 study intervention groups as described below. Participants will remain on their assigned study intervention through Week I 12.
Guselkumab Induction Dose Regimen
Selection of the Phase 3 guselkumab induction dose for Induction Study 2 will be based on an interim analysis of Induction Study 1. The participants will receive study intervention at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).
At Week I-12, subsequent study intervention will be based on clinical response status as follows:

* Guselkumab clinical responders at Week I-12: Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
* Guselkumab clinical nonresponders at Week I-12: Participants will receive guselkumab 200 mg SC at Weeks I-12, I-16, and I-20. Placebo IV will also be administered at Weeks I 12, I 16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:
* Guselkumab clinical responders at Week I-24 (ie, guselkumab 24 week respônders): Participants will enter the Maintenance Study and will receive guselkumab 200 mg SC q4w.
* Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Placebo

Participants will receive placebo IV at Weeks I-0, I-4, and I-8 (ie, 3 IV doses).

At Week I-12, subsequent study intervention will be based on clinical response status as follows:
* Placebo clinical responders at Week I-12: Participants will enter the Maintenance Study and receive placebo SC q4w.
* Placebo clinical nonresponders at Week I-12: Participants will receive the Phase 3 guselkumab induction IV dose at Weeks I-12, I-16, and I-20. Placebo SC will also be administered at Weeks I-12, I-16, and I-20 to maintain the blind.

At Week I-24, subsequent study intervention will be based on clinical response status as follows:
* Guselkumab clinical responders at Week I-24 (ie, placebo crossover responders): Participants will enter the Maintenance Study and will be rerandomized to either receive guselkumab 200 mg SC q4w, guselkumab 100 mg q8w, or placebo.
* Guselkumab clinical nonresponders at Week I-24: Participants will discontinue study intervention.

Maintenance Study (Phase 3 Maintenance Study)

In the Maintenance Study, the randomized population (ie, the primary analysis population) will include guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 from Induction Study 1 or Induction Study 2. These participants will be rerandomized to 1 of 3 study intervention groups as described below.
* Guselkumab 200 mg SC q4w: Participants will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44.
* Guselkumab 100 mg SC q8w: Participants will receive guselkumab 100 mg SC q8w starting at Week M-4 through Week M-44. Placebo SC will also be administered at alternate visits to maintain the blind.
* Placebo: Participants will receive placebo SC q4w starting at Week M-0 through Week M 44.

Participants will remain on their assigned study intervention through Week M-44. Participants who subsequently meet criteria for loss of clinical response

will be eligible for a single blinded dose adjustment as described in the protocol.
In the Maintenance Study, the nonrandomized population will consist of delayed responders to guselkumab at Week I-24 and placebo responders at Week I-12. Delayed responders to guselkumab at Week I-24 will receive guselkumab 200 mg SC q4w starting at Week M-0 through Week M-44. Placebo responders at Week I-12 will receive placebo SC q4w starting at Week M-0 through Week M-44. These populations are not eligible for dose adjustment.

Study burden and risks

Side effects (application) study medication, possible side effects/discomforts of the evaluations in the study, unknown risks.

Potential risks of guselkumab, including those of serious infection and malignancy, are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the studies. In addition, a comprehensive safety monitoring plan with oversight from an external, independent Data Monitoring Committee (DMC) will be implemented to ensure the safety of guselkumab in participants with moderately to severely active UC.

Contacts

Public
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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female, 18 years of age or older
2. Documented diagnosis of UC at least 3 months before screening
3. Moderately to severely active UC as defined by baseline modified Mayo score
4. History of inadequate response to or failure to tolerate conventional or advanced therapy as defined in the protocol
5. Screening laboratory test results within the study protocol defined parameters

Please see section 5.1 in the protocol for all inclusion criteria.

Exclusion criteria

1. Severe extensive colitis as defined in the study protocol
2. UC limited to the rectum only
3. Presence of a stoma
4. Presence or history of a fistula
5. Presence of symptomatic colonic or small bowel obstruction
6. History of extensive colonic resection
7. History of colonic mucosal dysplasia
8. Indeterminate colitis, microscopic colitis, ischemic colitis, or Crohn's disease or clinical findings suggestive of Crohn's disease.

Please see section 5.2 in the protocol for all exclusion criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tremfya
Generic name:	Guselkumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-09-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-03-2020

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2021

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	04033445
EudraCT	EUCTR2018-004002-25-NL
CCMO	NL70935.091.19