A Phase 3, Multicenter, Randomized, Platform Study of p19 Inhibition of the IL-23 Pathway to Establish Efficacy in Pediatric Crohn*s Disease;ISA title: A Phase 3, Multicenter, Randomized Clinical Study to Evaluate Mirikizumab in Pediatric Crohn*s Disease

Published: 10-01-2023
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2024-511472-32-00 check the CTIS register for the current data. Primary for Platform-Level Exploratory Analysis1. To evaluate whether treatment with IL-23 inhibitors is superior to adult placebo in...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON53427

Source
ToetsingOnline

Brief title
Macaroni-23-Eli Lilly

Condition

- Gastrointestinal inflammatory conditions

Synonym
Chron's disease - granulomatous enteritis

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly

Intervention

Keyword: Crohn's Disease, Efficacy, mirikizumab

Outcome measures

Primary outcome

Primary parameters for Platform-Level Exploratory Analysis

• Proportion of participants achieving clinical remission (PCDAI) at Week 52 AND

• Proportion of participants achieving endoscopic response (SES-CD) at Week 52

Primary global parameters

• Clinical remission at Week 52 (defined as PCDAI score <=10)

• Endoscopic response (>=50% reduction from SES-CD score at baseline) at Week 52

Secondary outcome

Global parameters

• Clinical response (decrease from baseline/LOR reference in the PCDAI score

>=12.5; total score <=30) at Week 12

• Clinical response (PCDAI) at Week 52

• Clinical remission (PCDAI) at Week 12

• Endoscopic remission (SES-CD) at Week 52

• Corticosteroid-free clinical remission at Week 52 (defined as PCDAI score <=10

at Week 52 and not receiving corticosteroids for at least 90 days before Week

52)

• Sustained clinical remission at Weeks 12, 24, and 52 (defined as PCDAI <=10 at

each of these timepoints)

• Clinical remission by PRO at:

* Week 12

* Week 52

* Week 12 and Week 52

• Serum mirikizumab concentration during induction from Week 0 through Week 12

• Serum mirikizumab concentration during maintenance (at least Ctrough)

• Change from baseline at Weeks 12, 24, and 52 in:

* Weight

* Weight percentiles and z-scores

* Height

* Height percentiles and z-scores

* Height Velocity

• AEs, including SAEs

• Clinical remission at Week 52 (defined as PCDAI score <=10)

• Endoscopic response (>=50% reduction from SES-CD score at baseline) at Week 52

Study description

Background summary

The basic pathogenesis of CD is similar in pediatric and adult populations (Van Limbergen 2008; Vernier-Massouille 2008). Both adult and pediatric CD can

affect any portion of the intestinal tract with focal, asymmetric, transmural, and granulomatous inflammation and is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis (Gajendran 2018; Rosen 2015; Torres 2017). Most commonly, children have ileocolonic involvement, and approximately one-third of children have upper tract involvement as well (Conrad 2017). In addition to the clinical similarities between adult and pediatric CD (eg, natural history, response to existing therapeutics), there is strong molecular genetic support for extrapolation of results in adults with CD to children. CD in both adults and children appears to result from complex interactions between evolving environmental changes induced by societal progress, predisposing genetic mutations, gut microbiota, and immune defense mechanisms (Kugathasan 2007).

The treatment of pediatric CD generally follows the same paradigms that are used to treat adult disease. The current standard of care involves anti-inflammatory therapeutic approaches, which include, corticosteroids, immunomodulatory agents (AZA, 6-MP, MTX), and TNF antagonist therapies. Per recent evidence- and consensus-based recommendations, the overall goals of treatment are similar in adults and children with CD: to induce short-term clinical response and to maintain disease remission with endoscopic response (Turner 2021). Responses to treatment are generally similar in adult and pediatric patients with CD based on available data (Van Limbergen 2008; Vernier-Massouille 2008).

Therefore, as in adults, there is a significant unmet medical need for additional safe and efficacious treatment options for children with CD. The lifelong course of the disease, and the lack of durable treatment highlights the need for additional options with a favorable benefit-risk profile.

The hypothesis for the platform-level exploratory analysis is that treatment response of pediatric
participants with moderately to severely active CD treated with an IL-23 inhibitor is superior to
that of adult participants with moderately to severely active CD administered placebo (based on adult placebo historical control data). The totality of evidence determining efficacy will be based on the intervention cohort-specific analyses with support of the exploratory platform analyses.

Study objective

This study has been transitioned to CTIS with ID 2024-511472-32-00 check the CTIS register for the current data.

Primary for Platform-Level Exploratory Analysis
1. To evaluate whether treatment with IL-23 inhibitors is superior to adult placebo in achieving clinical remission and endoscopic response in pediatric participants with moderately to severely active CD at Week 52 who do not

require modification of IP regimen, IP rescue therapy, or non-IP rescue therapy

Abbreviations: CD=Crohn*s disease; IL=interleukin, IP=investigational product; PCDAI=Pediatric Crohn*s Disease Activity pic Score for Crohn*s Disease.
Non-IP rescue therapy is CD medications not including study intervention (guselkumab or mirikizumab) as specified in the applicable ISA.

Primary global
2. To evaluate the clinical and endoscopic efficacy of mirikizumab in pediatric participants with CD at the end of maintenance therapy among participants who were in clinical response to mirikizumab at Week 12

Secondary
• To evaluate the clinical efficacy of mirikizumab in pediatric participants with CD
• To evaluate the efficacy of treatment with mirikizumab in clinical remission by PRObi at Week 12 and/or Week 52
Note: Depending on the participant*s age, can be PRO or ObsRO
• To evaluate the PK and immunogenicity of mirikizumab in pediatric participants with CD
• To assess the impact of mirikizumab therapy on growth
• To evaluate the safety of mirikizumab in pediatric participants with CD
• To evaluate the efficacy of treatment with mirikizumab in participants who are assigned at Week 12 to q4w maintenance therapy and do not receive non-investigational product (IP)c rescue therapy
• To further evaluate the clinical efficacy of mirikizumab in pediatric participants with CD
• To evaluate the efficacy of treatment with mirikizumab in inducing endoscopic remission at Week 52
• To assess the fistula response rate of mirikizumab therapy
• To assess the impact of mirikizumab therapy on CD-related QoL
• To explore serum and fecal biomarkers in pediatric participants with moderately to severely active CD
• To evaluate the efficacy of treatment with mirikizumab in inducing histologic remission at Week 52

Study design

This is a Phase 3 multicenter, randomized, 2-arm, intervention platform program to investigate the efficacy, safety, and PK of 2 different IL-23 inhibitors in pediatric CD. The platform program will use a treat-through* design and will assess induction and maintenance efficacy of 2 different IL-23 inhibitors guselkumab [JRD] or mirikizumab [Lilly]), with participants being followed from randomization through the safety follow-up visit for participants who do not enter the LTE (including early terminators), or Week 52 for patients who enter the LTE.

The 2 ISAs have separate sample size requirements (ranging from approximately 90 to 120 participants) to provide additional descriptive efficacy and safety data for the specific intervention, which are described in the applicable ISA.

The platform-level exploratory analysis is powered at N=50 randomized participants per intervention-specific platform cohort. Thus, the platform analysis set will have an adequate sample with at least 100 randomized participants (ie, at least 50 per intervention-specific platform cohort) to control for an acceptably low false positive and false negative rate for the platform-level coprimary endpoints.

The study population includes pediatric participants (2 to <18 years of age) with moderately to severely active CD (defined by a baseline PCDAI score >30) who have an inadequate response to, LOR to, or are intolerant to non-biologic therapy for CD (biologic-naïve, Bio-NF), and/or those who failed biologic and/or advanced therapy for CD (eg, biologic/JAK inhibitor-failed, Bio-IR).

Screening is to be performed prior to randomization to minimize imbalances between the intervention-specific platform cohorts in the enrolled participant populations due to differences in screen failures (if randomization to the intervention-specific platform cohort occurred prior to screening). If only 1 intervention cohort is open, participants will be assigned to that intervention cohort. In addition, stratification for the randomization of intervention cohort assignment to maintain comparable populations across intervention-specific platform cohorts will be used. Stratification factor(s) include prior biologic/JAK use and age (2 to <6, 6 to <12, 12 to <18 years of age).

Study periods will be as follows:
• The screening period will be up to 6 weeks.
• A 12-week induction period.
• A maintenance period from Week 12 to Week 52.
• A safety follow-up period as specified in the applicable ISA.

Study burden and risks

The clinical benefit of mirikizumab, an IL-23 antagonist, has been shown in a limited dataset in adults with moderately to severely active CD, and is being further evaluated in an ongoing Phase 3 study. A compound with a similar mechanism of action affecting the same pathway, ustekinumab (an antagonist of IL-12 and IL-23), has been approved for the treatment of CD in adults. Ustekinumab has also been studied in a Phase 1 pediatric CD study, CNTO1275CRD1001 (UniStar), and in an ongoing pediatric CD Phase 3 study (CNTO1275CRD3004; UNITI, Jr). In CNTO1275CRD1001, serum ustekinumab concentrations observed in the overall pediatric CD population were generally comparable to those observed in the reference adult CD population (with lower

serum concentrations in participants with body weight <40 kg). Also, at Week 8, ustekinumab induction treatment resulted in meaningful improvements in the efficacy endpoints evaluated, including PCDAI-based clinical response and clinical remission (Rosh 2021).
While the CNTO1275CRD1001 results with a compound with a similar mechanism of action are suggestive that mirikizumab should be effective in pediatric CD, the clinical benefit of mirikizumab remains to be seen in pediatric participants as the clinical development program is ongoing. While it is possible that participants in this study may not benefit from the study intervention, the results from the GALAXI 1 IA suggests the clinical benefit of mirikizumab. The sponsor anticipates that pediatric participants with CD may benefit from treatment with mirikizumab. Participants may also have some benefit from the participation in a clinical study irrespective of receiving study intervention, due to regular visits and assessments monitoring their overall health. Lastly, while not directly benefiting the participant, results from this clinical study will inform on the overall safety and efficacy of mirikizumab in treating moderately to severely active CD in pediatric participants ages 2 to <18, which would benefit other pediatric patients with CD.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. 2 to <18 years of age, inclusive (at the time of consent for screening).
2. Medically stable based on physical examination, medical history, and vital signs
performed at screening. Medically stable based on clinical laboratory tests performed at
screening.
3. Have a diagnosis of CD or fistulizing CD, with active colitis, ileitis, or ileocolitis,
confirmed at any time in the past by clinical, endoscopic, and histologic criteria.
Diagnosis based on prior surgical resection and histology is also acceptable. Radiographic
findings may provide supportive evidence.
4. Have moderately to severely active CD (as defined by a screening PCDAI score >30).
5. Have endoscopy with evidence of active CD defined as SES-CD score >=6 (or >=4 for
participants with isolated ileal disease) within 4 weeks of receiving study intervention
at Week 0.
6. Body weight >=10 kg at the time of consent for screening.

Please refer to the Master protocol for more inclusion criteria, section 5.1.

Exclusion criteria

1. Has complications of CD such as symptomatic strictures or stenosis, short gut syndrome, or any other manifestation that might be anticipated to require surgery, that could preclude the use of the PCDAI to assess response to therapy or would possibly confound the ability to assess the effect of the treatment. Of note, surgical procedures related to fistula treatment are not necessarily exclusionary; discuss with medical monitor.
2. Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to Week 0, or 8 weeks prior to Week 0 for intra-abdominal

abscesses, provided that there is no anticipated need for any further surgery.
3. Has had any kind of bowel resection within 26 weeks or any other intra-abdominal surgery within 12 weeks of baseline.
4. Presence of a stoma, ileoanal pouch, or ostomy.
5. Has high grade dysplasia, history of or current evidence of polypoid or non-polypoid dysplasia, or any adenoma that has not been removed.
Please refer to the Master protocol for more exclusion criteria, section 5.2

Study design

Design

Study phase:	3
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2023
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	mirikizumab
Generic name:	mirikizumab

Ethics review

Approved WMO

Date:	10-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2024-511472-32-00
EudraCT	EUCTR2022-000811-29-NL
CCMO	NL83188.056.22