A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in complement 3 glomerulopathy

Published: 03-09-2021
Last updated: 25-09-2024

This study has been transitioned to CTIS with ID 2023-509331-83-00 check the CTIS register for the current data. Primary objective adults:To demonstrate the superiority of iptacopan (200 mg b.i.d.) compared to placebo in reducing proteinuria at 6...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON56053

Source
ToetsingOnline

Brief title
CLNP023B12301 (APPEAR-C3G)

Condition

- Nephropathies

Synonym
Complement Kidney Disease, Nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: C3 Glomerulopathy, Chronic Kidney Disease, iptacopan, LNP023

Outcome measures

Primary outcome

In adults and adolescents:

• Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine

collection) at 6 months.

In adults and adolescents Open Label phase:

• Change from baseline in log-transformed UPCR at the 12-month visit (both

study treatment arms).

• Change in log-transformed UPCR from the 6-month visit to the 12-month visit

in the placebo arm.

Secondary outcome

In adults:

• Change from baseline in eGFR at 6 months.

• A participant meets the requirements of the composite renal endpoint if

he/she satisfies the following criteria at the 6-month time point: (1) a stable

or improved eGFR compared to the baseline visit (<=15% reduction in eGFR), and

(2) a >=50% reduction in UPCR compared to the baseline visit. Initiation of

treatment with any complement pathway modifying agent or

initiation/intensification of corticosteroid or immunosuppressant or renal replacement therapy automatically designates the participant as not meeting the endpoint.

• Change from baseline in disease total activity score in a renal biopsy at 6 months.

• Change from baseline to 6 months in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score.

• Occurrence of clinically significant vital signs (msDBP, msSBP, heart rate), ECGs, and safety laboratory measurements, as well as adverse events (AEs), AEs of special interest, and study drug discontinuation due to an AE (or any safety issue) during the double-blind period of the study.

In adolescents:

• Change from baseline in eGFR at 6 months.

• A participant meets the requirements of the composite renal endpoint if he/she satisfies the following criteria at the 6-month time point: (1) a stable or improved eGFR compared to the baseline visit (<=15% reduction in eGFR), and (2) a >=50% reduction in UPCR compared to the baseline visit. Initiation of treatment with any complement pathway modifying agent or initiation/intensification of corticosteroid or immunosuppressant or renal replacement therapy automatically designates the participant as not meeting the endpoint.

• Change from baseline to 6 months in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score.

• Occurrence of clinically significant vital signs (msDBP, msSBP, heart rate), ECGs, and safety laboratory measurements, as well as adverse events (AEs), AEs of special interest, and study drug discontinuation due to an AE (or any safety issue) during the double-blind period of the study.
• Evaluation of iptacopan*s potential effects on heart rate, systolic and diastolic blood pressures, cardiac function and a cardiac biomarker throughout the double-blind and open- label treatment periods.

Open Label phase adults and adolescents:
• A participant is defined as meeting the requirements of the composite renal endpoint if they satisfy the eGFR and UPCR criteria at the 12-month time point (both treatment arms).
The rate of this endpoint will also be evaluated in the placebo arm at the 12-month visit compared to the 6-month visit.
• Only adults: Change from baseline in the total activity score in a renal biopsy at 12 months (both study treatment arms).
Change in the total activity score in a renal biopsy from the 6-month visit to the 12-month visit of the placebo arm.
• Change from baseline in the FACIT-Fatigue score at 12 months (both study treatment arms).
Change in the FACIT-Fatigue score from the 6-month visit to the 12-month visit of the placebo arm.
• Occurrence of clinically significant vital signs (msDBP, msSBP, heart rate), ECGs, and safety laboratory measurements, as well as adverse events (AEs), AEs

of special interest, and study drug discontinuation due to an AE (or any safety

issue) during the open-label period of the study (and combined with the

double-blind period).

Study description

Background summary

The purpose of this Phase 3 study is to evaluate the efficacy and safety of iptacopan compared to placebo (and standard of care) in patients (adults and adolescents) with native C3G. Adult and adolescent participants will be randomized independently and separate analyses will be conducted in the adult and adolescent cohorts. The study aims to demostrate a reduction in proteinuria and improvement in estimated Glomerular Filtration Rate (eGFR) in participants treated with iptacopan compared to placebo. Kidney biopsies will be performed in adults only to assess histopathological reductions in glomerular inflammation and Complement 3 (C3) deposition, and improvement in fatigue will be evaluated. Complement alternative pathway (AP) dysregulation is believed to underlie the clinical manifestations and progression of C3G. Serum C3 and other complement pathway biomakers will be assessed to demonstrate that ipatacopan reduces AP activity and targets the underlying cause of disease.

Study objective

This study has been transitioned to CTIS with ID 2023-509331-83-00 check the CTIS register for the current data.

Primary objective adults:
To demonstrate the superiority of iptacopan (200 mg b.i.d.) compared to placebo in reducing proteinuria at 6 months of treatment.
The primary clinical question of interest is:
What is the effect of iptacopan vs. placebo on log-transformed ratio to baseline in urinary protein/creatinine ratio (UPCR, sampledfrom a 24-hour urine collection) at 6 months.

Primary objective adolescents:
To evaluate the effect of iptacopan on proteinuria at 6 months treatment.

Primary objective open-label treatment period adults and adolescents:
To evaluate the effect of iptacopan on proteinuria at 12 months.

Secundary objective adults:

To demonstrate the superiority of iptacopan vs. placebo in improving eGFR by assessing the change from baseline in eGFR at 6months.
To demonstrate the superiority of iptacopan vs. placebo in the proportion of participants who achieved the composite renal endpoint.A participant meets the requirements of the composite renal endpoint if he/she satisfies the following criteria at the 6-month timepoint: (1) a stable or improved eGFR compared to the baseline visit (<=15% reduction in eGFR), and (2) a >=50% reduction in UPCRcompared to the baseline visit. Initiation of treatment with any complement pathway modifying agent or initiation/intensification ofcorticosteroids or immunosuppressants or renal replacement therapy automatically designates the participant as not having met theendpoint.
To demonstrate the effect of iptacopan vs placebo in reducing glomerular inflammation in the kidney by assessing the change frombaseline in disease total activity score in a renal biopsy at 6 months.
To assess the effect of iptacopan compared to placebo in improvement of patient-reported fatigue by assessing the change frombaseline to 6 months in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score.
To evaluate the safety and tolerability of iptacopan compared to placebo during the 6-month double-blind period by assessing theoccurrence of clinically significant vital signs, Electrocardiograms (ECGs), and safety laboratory measurements, as well as adverseevents (AEs), AEs of special interest, and study drug discontinuation due to an AE (or any safety issue) during the double-blindportion of the study.

Secundary objective adolescents:
To evaluate the effect of iptacopan in improving eGFR by assessing the change from baseline in eGFR at 6 months.
To evaluate the effect of iptacopan on a composite renal endpoint. A participant meets the requirements of the composite renal endpoint if he/she satisfies the following criteria at the 6-month time point: (1) a stable or improved eGFR compared to the baseline visit (<=15% reduction in eGFR), and (2) a >=50% reduction in UPCR compared to the baseline visit. Initiation of treatment with any complement pathway modifying agent or initiation/intensification of corticosteroids or immunosuppressants or renal replacement therapy automatically designates the participant as not having met the endpoint.
To evaluate the effect of iptacopan in improvement of patient-reported fatigue by assessing the change from baseline to 6 months in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score.
To evaluate the safety and tolerability of iptacopan compared to placebo during the 6-month double-blind period by assessing the occurrence of clinically significant vital signs, Electrocardiograms (ECGs), and safety laboratory measurements, as well as adverse events (AEs), AEs of special interest, and study drug discontinuation due to an AE (or any safety issue) during the double-blind portion of the study.
Additional CV safety surveillance: the evaluation of iptacopan*s potential

effects on heart rate, systolic and diastolic blood pressures, cardiac function and a cardiac biomarker throughout the double-blind and open- label treatment periods.

Secundary objective open-label treatment period adults and adolescents:
To evaluate the effect at 12 months of iptacopan on a composite renal endpoint, in reducing glomerular inflammation in the kidney and in improvement of patient reported fatigue.
To evaluate the safety and tolerability of iptacopan during the 6-month open-label treatment period as well as the entire 12-month treatment period.

Study design

This study is a multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan in patients with native C3G. Approximately 68 adult and 15 adolescent participants will be randomized in the trial (adult and adolescent cohorts will be analyzed separately). Half of the adult participants (n=34) will receive iptacopan at 200 mg b.i.d. as blinded treatment for 6 months followed by 6 months of open-label iptacopan at 200 mg b.i.d. The other half of participants (n=34) will receive placebo as blinded treatment for 6 months followed by 6 months of open-label iptacopan at 200 mg b.i.d. Adolescent participants will be randomized 2:1 with approximately 10 receiving iptacopan at 200 mg b.i.d. as blinded treatment for 6 months followed by 6 months of open-label iptacopan at 200 mg b.i.d. The other approximately 5 participants will receive placebo as blinded treatment for 6 months followed by 6 months of open-label iptacopan at 200 mg b.i.d. Upon completion of study treatment at 12 months, participants will have the option to discontinue iptacopan treatment and enter a Safety Follow-up period or continue open-label iptacopan treatment by transitioning to a C3G Extension study.

Intervention

Adult participants will be randomized to one of the two treatment arms in a 1:1 ratio.
• Iptacopan arm: Iptacopan orally at 200 mg b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months
• Placebo arm: Placebo orally for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months

Asolescent participants will be randomized to one of the two treatment arms in a 2:1 ratio.
• Iptacopan arm: Iptacopan orally at 200 mg b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months
• Placebo arm: Placebo orally for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months

Study burden and risks

Infections due to the effect of LNP023 on the immune system
Delayed maturation of sperm, not observed in humans to date
Damage to the bone marrow and anemia, not observed in humans at lower doses
Thyroid disorders, so far not observed in humans
Cardiac effects: hemodynamic and long term morphological changes (observed only in juvenile dog toxicity studies

Vaccination 1-3x against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae
Physical examination 10x
Vital signs 10x
Blood and urine test 10x
24 hour urine collection 4x
Morning urine 10x
Kidney biopsy (adults only)
ECG 4x
Questionnaires 8x
Keep a diary: daily
Tanner puberty scale 2x (adolescents only)
7 hours cardiovascular surveillance 2x (adolescents only)
Echocardiography 5x (adolescents only)
Home (55x) and ambulant 24 hour monitoring (3x) of blood pressure and heart rate (adolescents only)
Optional, additional exploratory capillair blood sampling 2x (adolescents only)

Contacts

Public
Novartis

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Amsterdam 1101 BX
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Scientific
Novartis

Haaksbergweg 16
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

Male and female participants age >= 18 and <= 60 years (adult cohort) or age >= 12 and <=
17 years (adolescent cohort) at screening.

Diagnosis of C3G as confirmed by renal biopsy within 12 months prior to enrollment in adults and within 3 years of enrollment in adolescents (a biopsy report, review and confirmation by the Investigator is required). If such a biopsy is not available, confirmation may be obtained using tissue from the Day -45 biopsy (adults only) for local assessment (tissue may be processed, evaluated, and reported by Arkana Laboratories but eligibility is determined by the Investigator).

Prior to randomization, all participants must have been on a maximally recommended or tolerated dose of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for at least 90 days. The doses of other antiproteinuric medications including mycophenolic acids, corticosteroids and mineralocorticoid receptor antagonists should be stable for at least 90 days prior to randomization.

Reduced serum C3 (defined as less than 0.85 x lower limit of the central laboratory normal range) at Screening.

UPCR >= 1.0 g/g sampled from the first morning void urine sample at Day -75 and Day -15.

Estimated GFR (using the CKD-EPI formula for adults and modified Schwartz formula
for adolescents) or measured GFR >= 30 ml/min/1.73m2 at screening and Day -15.

Mandatory vaccination against Neisseria meningitidis and Streptococcus Pneumoniae infection prior to the start of study treatment. If the patient has not been previously vaccinated, or if a booster is required, the vaccine should be given according to local regulations at least 2 weeks prior to the first administration of study treatment. If study treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should be initiated.

If not previously vaccinated, or if a booster is required, vaccination against Haemophilus influenzae infections should be given, if available and according to local regulations, at least 2 weeks prior to the first study treatment administration. If study treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should be initiated.

Exclusion criteria

• Participants who have received any cell or organ transplantation, including kidney transplantation. • Rapidly progressive crescentic glomerulonephritis defined as a 50% decline in the eGFR within 3 months) with renal biopsy findings of glomerular crescent formation seen in at least 50% of glomeruli. • Renal biopsy showing interstitial fibrosis/tubular atrophy (IF/TA) of more than 50%. • Monoclonal gammopathy of undetermined significance (MGUS) confirmed by the measurement of serum free light chains or other investigation as per local standard of care. • Participants with an active systemic bacterial, viral or fungal infection within 14 days prior to study treatment administration or the presence of fever >= 38°C (100.4°F) within 7 days prior to study treatment administration. • A history of recurrent invasive infections caused by encapsulated organisms, e.g., meningococcus or pneumococcus. • The use of inhibitors of complement factors (e.g., Factor B, Factor D, C3 inhibitors, anti Complement 5 (C5) antibodies, C5a receptor antagonists) within 6 months prior to the Screening visit. • The use of immunosuppressants (except mycophenolic acids), cyclophosphamide or systemic corticosteroids at a dose >7.5 mg/day (or equivalent for a similar medication) within 90 days of study drug administration. The use of mycophenolic acids is not permitted within 90 days prior to randomization in India. Acute post-infectious glomerulonephritis at screening based upon the opinion of the Investigator.

Study design

Design

Study phase: 3

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-03-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet bekend
Generic name:	iptacopan

Ethics review

Approved WMO Date:	03-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	22-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2023
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2023
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	CTIS2023-509331-83-00
EudraCT	EUCTR2020-004589-21-NL
ClinicalTrials.gov	NCT04817618
CCMO	NL77639.056.21