A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTINATIONAL, MULTICENTER STUDY WITH OPEN-LABEL TREATMENT EXTENSION TO ASSESS THE EFFECT OF MIN-102 ON THE PROGRESSION OF ADRENOMYELONEUROPATHY IN MALE PATIENTS WITH X-LINKED ADRENOLEUKODYSTROPHY

Published: 10-07-2017
Last updated: 16-11-2024

Main StudyPrimary efficacy objective: To evaluate the efficacy of MIN-102 on the progression ofadrenomyeloneuropathy (AMN) in male patients as determined by the change from baseline in Six-Minute Walk Test (6MWT) compared with placebo after 96 weeks...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON56243

Source
ToetsingOnline

Brief title
Minoryx MT-2-01

Condition

- Neurological disorders NEC

Synonym
Neurological disease; genetic disorder

Research involving
Human

Sponsors and support

Primary sponsor: Minoryx Therapeutics S.L.
Source(s) of monetary or material Support: Minoryx Therapeutics S.L.

Intervention

Keyword: Adrenomyeloneuropathy, MIN-102, X-Linked Adrenoleukodystrophy

Outcome measures

Primary outcome

Main Study:

The primary endpoint for the main study is the change from baseline to Week 96

in total walking distance in the 6MWT.

Extension Study

Safety

The primary endpoint of the extension study is long-term safety and

tolerability of MIN-102, which will be assessed in terms of:

• AEs

• SAEs and SUSARs

• Vital signs (body weight, blood pressure, pulse rate)

• 12-lead ECG

• Clinical laboratory tests (hematology, blood chemistry including parameters for adrenal function, urinalysis and sample for cytology).

Secondary outcome

Main Study

Secondary efficacy endpoints are changes from baseline to week 96 in the following:

• Body sway amplitude (in four states: eyes closed/feet apart, eyes open/feet apart, eyes closed/feet together, eyes open/feet together)

• SSPROM

• EDSS

• Clinical Global Impressions - Severity (CGI-S)

• Clinical Global Impressions - Improvement (CGI-I)

• Patient Global Impressions - Improvement (PGI-I)

• Dynamometry

• Quality of Life Assessments

- European Quality of Life 5 Dimensions (EQ-5D-5L)

- Multiple Sclerosis Walking Scale (MSWS-12)

- Qualiveen Short Form quality of life questionnaire for urinary disorders (Qualiveen-SF)

- International Index of Erectile Function questionnaire (IIEF)

• Incidence of progression of cerebral lesions

- Defined as:

- Incidence of inflammatory lesions, or

- Growth of existing non-inflammatory lesions since Screening or Baseline, or

- Occurrence of new non-inflammatory lesions after Screening or Baseline

• Loes severity score on the MRI

Exploratory endpoints comprise assessment of changes from baseline to week 96 in:

• Biomarkers in plasma

• Biomarkers in CSF

• Biomarkers in the spinal cord (through MRS)

• Brain and spinal cord MRI

Pharmacokinetic variables are:

• MIN-102 and M3 concentrations in plasma (all patients) and CSF (at one site in The Netherlands).

Safety will be assessed in terms of:

• Adverse events (AEs)

• Serious adverse events (SAEs) and suspected unexpected serious adverse drug reactions (SUSARs)

• Vital signs (body weight, blood pressure, pulse rate and body temperature)

• 12-lead electrocardiogram (ECG)

• Clinical laboratory tests (hematology, blood chemistry including parameters for adrenal function, urinalysis and sampling for cytology).

Extension Study:

Efficacy

The efficacy endpoints are the changes from the baseline of Part 2 (V6) to the

last scheduled on-study assessment for the following variables:

• 6MWT (only through to end visit 11)

• Body sway amplitude (in four states: eyes closed/feet apart, eyes open/feet

apart, eyes closed/feet together, eyes open/feet together)

• SSPROM

• EDSS

• Quality of Life Assessments (EQ-5D-5L, MSWS-12, Qualiveen-SF and IIEF)(only

through to end visit 11).

• Incidence of progression of cerebral lesions

- Defined as:

- Incidence of inflammatory lesions, or

- Growth of existing non-inflammatory lesions since Screening or Baseline, or

- Occurrence of new non-inflammatory lesions after Screening or Baseline

• Loes severty scores on the MRI

Study description

Background summary

The two main clinical phenotypes of Adrenoleukodystrophy (ALD) are the predominantly neurodegenerative adrenomyeloneuropathy (AMN) and inflammatory cerebral ALD (cALD). There is no authorized treatment for AMN. Hematopoietic (blood) stem-cell transplantation is used in some patients with cALD but no therapy is available for AMN patients. Corticosteroids are used to treat the adrenal insufficiency. Therapies for ALD generally aim to either reduce

hyperlipidemia or lower dietary Very long chain fatty acid (VLCFA) intake; however this approach fails to achieve a clinically relevant effect in terms of slowing ALD progression. This apparent disconnect between reduced VLCFA levels and functional outcome could result from the pathogenic cascade in ALD having already been triggered by the time of VLCFA increase. This would support the idea of targeting downstream events in the ALD pathologic cascade to stop disease progression. As neuroinflammation is a hallmark of cALD, MIN-102 may be effective at modulating this phenotype.
MIN-102, the M4 metabolite of pioglitazone, is an optimized peroxisome proliferator-activated receptor γ (PPARγ) agonist for the treatment of neurodegenerative and neuroinflammatory disorders that is able to achieve exposure levels sufficient to unfold the full spectrum of beneficial effects at safe and well tolerated doses. MIN-102 and other PPARγ agonists have demonstrated to decrease oxidative stress, promote neuronal survival, regeneration and growth, promote oligodendrocyte differentiation and myelin synthesis, and decrease inflammation.
MIN-102 has a simpler metabolic profile than pioglitazone with a lower risk for drug-drug interactions, shows higher blood-brain barrier penetration and was validated in several non-clinical experiments as a promising candidate to treat both phenotypes of ALD with a level of PPARγ engagement that cannot be achieved with pioglitazone

Study objective

Main Study
Primary efficacy objective: To evaluate the efficacy of MIN-102 on the progression of
adrenomyeloneuropathy (AMN) in male patients as determined by the change from baseline in Six-Minute Walk Test (6MWT) compared with placebo after 96 weeks of treatment.

Secondary efficacy objectives: To evaluate the effects of MIN-102 after 96 weeks of treatment on:
• Change from baseline in body sway amplitude (in four states: eyes closed/feet apart, eyes open/feet apart, eyes closed/feet together, eyes open/feet together)
• Comprehensive clinical rating scales (Severity Score System for Progressive Myelopathy [SSPROM] and Expanded Disability Status Scale [EDSS])
• Clinician and patient global impression of symptom severity and change
• Muscle strength
• Quality of life
• Incidence of progression of cerebral lesions.
• Loes severity score

Exploratory objectives- To evaluate the effects of MIN-102 on various biochemical markers in plasma and cerebrospinal fluid (CSF), and spinal cord imaging parameters

Safety objectives- To evaluate the safety and tolerability of MIN-102 compared with placebo.

Extension Study
Primary objective- To assess the safety and tolerability of MIN-102 upon long-term treatment.

Secondary objectives- To evaluate the long-term effects of MIN-102 on:
• Change from baseline in 6MWT and body sway (in four states: eyes closed/feet apart, eyes open/feet
apart, eyes closed/feet together, eyes open/feet together)
• clinical rating scales (SSPROM and EDSS)
• Quality of life
• Incidence of progression of cerebral lesions.

Exploratory objectives- To assess the long-term effects of MIN-102 on various biochemical markers in
plasma.

Study design

Main Study
This is a Phase II/III, randomized, double-blind, placebo-controlled, multicenter, two parallel-group study in male patients with the AMN phenotype of X-linked adrenoleukodystrophy (X-ALD), to assess the efficacy and safety of MIN-102 treatment. Study sites will consist of specialist referral centers experienced in the management of adrenoleukodystrophy (ALD).

Extension Study
This is an open-label treatment extension study starting immediately after the day of last treatment in the double-blind period at V6, after the patient signs the extension part ICF. Visit 6 after 96 weeks of double-blind treatment will simultaneously be the baseline visit of this treatment extension study part. All patients included in the extension study will receive a MIN-102 dose to achieve the pre-defined target plasma exposure. Dose adjustments to achieve the target plasma exposure will be allowed until informed by PK parameters obtained at week 12 (V8); after this, no further dose adjustments will be allowed. Patients who, at the end of the previous double-blind part (at V6) are on a dose of <=10 mL will start Part 2 with the same dose. All other patients will be reverted to a starting dose of 10 mL.

Intervention

Main Study:
MIN-102 (study drug): A liquid suspension that will be taken orally, preferably after breakfast at the same time of the day once-daily at a dose of 150 mg

MIN-102, with the option for dose modification based on plasma exposure data obtained 4 weeks and 12 weeks after first dose to achieve the target exposure of 200 µg.hr.mL-1.
Placebo: A liquid suspension with 1 dose per day to be taken orally at the same time of day, preferably after breakfast.

Extension Study:
MIN-102 (study drug): Starting dose is 10 mL for all patients on a dose of >10 mL at V6. Patients on a dose of <=10 mL at V6 will continue with the same dose, with the option of dose modification based on plasma exposure data obtained until Week 12 (V8) to achieve the pre-defined target plasma exposure of 200 µg.hr.mL-1.

Study burden and risks

Patients are asked to undergo procedures described in the tables on pages 15 - 18 of the study protocol. These
procedures include physical examination, vital signs, ECG, cerebral/spinal cord MRI, lumbar puncture for CSF, blood draw, 6 minutes walking test, dynamometry, completing questionnaire and diaries, answer questions of investigator and study team, administration of study drug.
Additionally, fertile patients who are sexuallyactive must consent to use total abstinence or an effective form of contraception with their sexual partners throughout participation in the study. Patients are also asked to inform their study doctor on their medication usage and change in health status.
MIN-102 is a metabolite of pioglitazone, an approved treatment for type II diabetes. The safety profile of MIN-102 can be considered to have been evaluated directly or indirectly during pioglitazone development. It is expected that the safety profile of MIN-102 is similar to that of pioglitazone. Known side effects of pioglitazone are fluid retention and weight increase. There are some suggestions that bladder cancer may be associated with long-term administration of pioglitazone; however, there were too few events of bladder cancer to establish causality to pioglitazone. Nonetheless, even if the potential risk is considered to be very low, patients urine samples during the study will be carefully investigated for the presence of abnormal cells. One other clinical study with MIN-102 has been conducted. This was a study in healthy male volunteers. Only one related adverse event (side effect) of mild severity, dysphagia (difficulty in swallowing), was reported with MIN-102 at the 90-mg dose in fasting (non-eating) condition. Four related events of mild headache and one event each of mild nausea and somnolence occurred at the 270-mg dose level in the fed condition (when MIN-102 was administered after a meal). All adverse events resolved completely. Patient may also experience discomfort while performing blood draw (i.e. pain swelling, bruising, risk of infection, etc.), lumbar puncture (i.e. pain in lower back, temporary pain or numbness to the legs, etc.), ECG (i.e. adhesive used for the electrodes from the ECG may irritate patient*s skin) and MRI scans

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Main (Part 1)
1. Provision of written informed consent to participate in the main study.
2. Male patients aged >=18 to <=65 years.
3. Diagnosis of ALD based on genetic testing.
4. Clinical evidence of spinal cord involvement, with an EDSS score between 2 and 6.
5. Ability to walk for 6 minutes, without or with rest, with usual walking aids (e.g. leg braces, cane or crutch).
6. Ability to stand on a force plate with closed eyes and with feet apart for a minimum of 20 seconds.
7. Either a normal brain MRI or a type-1 through type-5 pattern MRI abnormality in which the abnormality does not show presence of inflammation. Note: MRI is not required at V-1 if an MRI was obtained within the 6 months prior to the

first day of screening.
8. Normal adrenal function or appropriate steroid replacement if adrenal insufficiency is present.
9. Patients who are surgically sterilized. If not surgically sterilized, patients should be willing to use adequate contraception and not donate sperm from the first dose of the study medication until 90 days after the follow-up visit. Adequate contraception for the male patient (and his female partner, if of childbearing potential) is defined as hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence, in accordance with the lifestyle of the patient, is also acceptable., Extension (Part 2):
1. Completion of the entire 96-weeks double-blind period of the study (Part 1).
2. Provision of written informed consent to participate in the extension study part.
3. Normal adrenal function or appropriate steroid replacement if adrenal function has changed during the double-blind treatment phase.
4. The following inclusion criteria of Part 1 will be modified:
• age >=18 to <=65 years will no longer apply.
• EDSS score between 2 and 6 will no longer apply.
• Ability to walk for 6 minutes will no longer apply. If a patient is unable to walk for 6 minutes, the maximum time and walking distance will be recorded. If a patient is unable or refuses to walk at all, this will also be recorded.
• Ability to stand on a force plate with eyes closed and feet apart for a minimum of 20 seconds will no longer apply. If a patient is no longer able to stand on a force plate for 20 seconds, this test will not be conducted.
• Either a normal brain MRI or a type-1 through type-5 pattern MRI abnormality in which the abnormality does not show presence of inflammation (gadolinium enhancement) will no longer apply.
In case of brain MRI lesions making the patient eligible for HSCT, he is still eligible for the extension study, but treatment will be discontinued immediately before any transplant-related treatment is initiated.
• A stable dose of Lorenzo*s Oil, botulinum toxin, N-acetylcysteine, baclofen, benzodiazepines, opiates and cannabis preparations, fampidrine, and antioxidants will no longer apply.
All other inclusion criteria of Part 1 remain in place.

Exclusion criteria

1. Any other chronic neurological disease with signs of spastic paraplegia, such as hereditary spastic
paraplegia, multiple sclerosis, etc.
2. Presence of inflammatory (Gd-enhancing) MRI lesions or any abnormality other than those mentioned in the inclusion criteria.
3. Known type 1 or type 2 diabetes.

4. Known intolerance to pioglitazone or any other thiazolidinedione.
5. Patients who are taking or have taken honokiol, pioglitazone or other thiazolidinediones within the 6 months prior to screening.
6. Patients who are taking biotin (MD-1003) or have taken biotin within the 3 months prior to screening
7. Patients who are taking Lorenzo's oil unless the dose has been stable for at least 6 months prior to screening and is kept stable during the Part 1 of study.
8. Participation in a previous clinical study with antioxidants (such as N-acetylcysteine, lipoic acid and
vitamin E) within the 6 months prior to screening. Note: antioxidants will be allowed during this study if the dose has been stable for at least 6 months prior to screening and is kept stable until the end of Part 1.
9. Previous bone marrow transplantation.
10. Current treatment with immunosuppressant medication, except for corticosteroids.
11. A requirement for treatment with a prohibited concomitant medication
12. Previous or current history of cancer (other than treated basal cell carcinoma).
13. Previous or current history of congestive heart failure.
14. Reduced left-ventricular ejection fraction, or other clinically significant cardiac abnormalities on echocardiogram that in the investigator*s opinion could predispose the subject to volume overload or its attendant consequences.
15. A positive result on laboratory tests for hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody.
16. Patients with clinically significant anemia (hemoglobin <12.5 g/dL).
17. 15.17. Abnormal liver enzyme tests for aspartate transaminase (AST) or alanine transaminase (ALT) of >2x the upper limit of normal (ULN) or total bilirubin >1.5x ULN (unless due to Gilbert*s syndrome).
18. A value of B-type natriuretic peptide (BNP) of >150 pg/mL at Screening
19. Moderate or severe hepatic impairment (Child-Pugh classification groups B or C).
20. Chronic kidney disease (CKD) of stage 3 or higher (according to the Renal Association CKD staging).
21. Pulmonary or cardiac disease of sufficient severity to limit efficacy evaluation.
22. Cognitive or behavioral abnormalities that could impair the capacity to give informed consent or carry out protocol-specified procedures.
23. Contraindications for MRI such as having paramagnetic material in the body (e.g. aneurysm clips, pacemakers, intraocular metal or cochlear implants).
24. Current drug abuse, including recreational use, or addiction and/or alcohol abuse as evidenced by patient history or by a positive urine drug screen for opiates, methadone, cocaine, amphetamines (including ecstasy), cannabinoids, or barbiturates at V-1. Use of prescribed opiates and medically sanctioned use of cannabis oil is permitted.
25. Conditions that could modify absorption of the study drug.
26. Inability or unwillingness to comply with the study protocol.
27. Current suicidal ideation with an intention or plan to act, or a previous

suicide attempt.
28. Current participation in another clinical study.
29. Other medical, neuropsychiatric, or social conditions that, in the opinion of the investigator, are likely to adversely affect the risk-benefit of study participation, interfere with study compliance, or confound the study results.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-01-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MIN-102
Generic name:	5-[[4-[2-[5-(1-Hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]-2,4- thiazolidinedione hydrochloride

Ethics review

Approved WMO

Date:	10-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	03-05-2023
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Approved WMO
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Application type: Amendment

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Approved WMO
Date: 28-08-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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Approved WMO
Date: 27-09-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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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
EudraCT	EUCTR2017-000748-16-NL
CCMO	NL61934.018.17