Supplement

eMethods

Inclusion Criteria

Only patients who meet all of the following criteria will be eligible for inclusion in the study:

1. Signed informed consent by the patient or parent/legal guardian, and/or consent or assent for minors as required by national laws.
2. Male and female participants aged ≥12 and ≤60 years, inclusive, with Friedreich's Ataxia confirmed by genetic testing.
3. Total score on Scale for the Assessment and Rating of Ataxia (SARA) of <25.
4. Score on SARA item 1 (gait) ≥2 and ≤6.
5. Male with a potentially fertile partner must be willing to use an acceptable method of contraception for the duration of the study and for 3 months after study drug discontinuation (acceptable methods are: use of a condom with spermicide or use of oral, implantable or injectable contraceptives, or intrauterine devices, or a diaphragm with spermicide or diaphragm with condom) or have had a vasectomy.
6. Female with childbearing potential must be willing to use highly effective contraceptive methods during screening, during the period of drug administration and for 30 days after stopping study drug administration. Highly effective contraception methods include the following:
    - Total abstinence (defined as refraining from heterosexual intercourse during the entire period outlined above).
    - Male or female sterilization.
        - Bilateral tubal occlusion.

- Vasectomized partner.

- Use of at least one of the following:

  a. Oral, injectable, transdermal, intravaginal, or implantable hormonal methods of contraception.

  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable.

  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

7. Female patients of childbearing potential must have a negative serum pregnancy test result within 7 days before first administration of study drug.

Exclusion Criteria

Participants will be excluded from the study if they meet any of the following criteria:

1. Age of onset of disease ≥25 years.
2. Left ventricular ejection fraction (LVEF) <55%, on echocardiogram.
3. History of heart failure. Ventricular arrhythmia, supraventricular tachycardia, or having a QTcF time of >480 msec in 3 consecutive ECG recordings taken at least 5 minutes apart.
4. Known intolerance to pioglitazone or other thiazolidinediones.
5. Currently taking or have taken pioglitazone, or other thiazolidinediones, within the past 6 months prior to screening.

6. Currently participating in or having participated in another interventional clinical study within 2 months prior to screening.

7. Requiring other prohibited concomitant medication. Note: use of idebenone, coenzyme Q10, antioxidants, riboflavin, thiamine, vitamins C and E is permitted provided the dose has been constant for ≥3 months before screening and is kept constant during the entire study.

8. Previous or current history of vesical polyps, bladder cell hyperplasia, or bladder cancer.

9. Previous or current history of other cancer, unless surgically resected and without evidence of recurrence for a minimum of 5 years.

10. Clinically significant anemia (i.e., hemoglobin <110 g/L).

11. Glycated hemoglobin (HbA_{1c}) levels >6.4% and fasting blood glucose levels ≤0.9 times the lower limit of normal and ≥1.1 times the upper limit of normal.

12. *N*-terminal pro B-type natriuretic peptide level (NT-pro BNP) >125 pg/mL.

13. Abnormal liver enzyme tests for aspartate aminotransferase or alanine aminotransferase of >2 times the upper limit of normal or total bilirubin >1.5 times the upper limit of normal (unless due to Gilbert's syndrome).

14. A positive result on laboratory tests for hepatitis B surface antigen, hepatitis C antibody, and HIV antibody at screening.

15. Moderate or severe hepatic impairment (groups B and C according to the revised Child-Pugh classification).

16. Chronic kidney disease (CKD) stages 3a or higher (according to CKD staging by Renal Association with an estimated glomerular filtration rate of <60 mL/min/1.73m^2).

17. Contraindications for magnetic resonance spectroscopy (MRS) and MRI procedure such as participants with ferromagnetic materials in the body, such as dental braces, spinal rods, aneurysm clips, pacemakers, intraocular metal, or cochlear implants.
18. Drug or alcohol abuse in the past 2 years by subject history and/or investigator assessment.
19. Conditions that could modify the absorption of the study drug, such as inflammatory bowel diseases, or stomach or intestinal resection.
20. Inability or unwillingness of the subject or subject's parents or caregivers to comply with the study procedures.
21. Other medical, neurological, psychiatric, or social conditions that in the investigator's opinion are likely to confound the assessment of safety or efficacy, interfere with study conduct, or unfavorably alter the risk-benefit of subject participation.
22. Pregnant women as confirmed by a positive blood hormonal test.
23. Female patients intending to breast-feed a child while taking study drug or have taken study drug within 30 days after administration of the last dose.

MRI and MRS Acquisition and Processing

MRI and MRS Acquisition

Data were acquired on three Tesla Siemens MAGNETOM Prisma scanners (Siemens Healthineers AG, Erlangen, Germany) at three of the study sites using body coil transmit and a 64-channel head-neck receive coil. The fourth site utilized a three Tesla Siemens MAGNETOM Skyra scanner (Siemens Healthineers AG, Erlangen, Germany) using body coil transmit with a 20-channel head-neck receive coil for the spinal cord portion of the exam and a 32-channel head receive coil for the brain portion of the exam.

Brain Imaging Protocol

3D sagittal T1-weighted MPRAGE images (T_R = 2530 ms, T_E = 3.65 ms, T_I = 1100 ms, flip angle = 7°, voxel size = 1 mm isotropic, field of view (FOV) = 256 × 240 mm^2) and 3D sagittal T2-weighted SPACE images (T_R = 3200 ms, T_E = 564 ms, flip angle = 120°, voxel size = 1 mm isotropic, FOV = 256 × 240 mm^2) were acquired for morphometric analyses.

Diffusion data were acquired along 92 directions with an echo-planar spin-echo sequence (T_R = 3230 ms, T_E = 89.2 ms, flip angle = 78°, voxel size = 1.5 mm isotropic, FOV = 210 × 210 mm^2, multiband acceleration factor = 4, *b*-values = 1500 s/mm^2 and 3000 s/mm^2) and interleaved with 7 nondiffusion weighted images (*b*-value = 0 s/mm^2). The acquisition was repeated with the opposite phase-encoding scheme. Data were harmonized by matching the MR acquisition parameters as much as possible. For brain T1 (used for spine morphometry) and QSM, the parameters were identical across all sites. For brain diffusion, parameters were slightly different on the Skyra due to its less-performant gradient. To account for this difference, the following parameters were used for acquisition of diffusion data on the Skyra scanner: T_R = 3366 ms, T_E = 102.4 ms, flip angle = 78°, voxel size = 1.7 mm isotropic, FOV = 221 × 221 mm^2, multiband acceleration factor = 4, *b*-values = 1000 s/mm^2 and 2000 s/mm^2.

To estimate the degree of biometal accumulation, particularly brain iron, quantitative susceptibility mapping (QSM) was applied to the dentate nuclei (DN). Multi-echo gradient-echo images (T_R = 54 ms, number of echoes = 5, variable T_E = [9.84, 19.84, 29.52, 39.36, 49.20] ms, flip angle = 18°, voxel size = 0.9 mm isotropic, FOV = 230 × 230 mm^2) were acquired in the cerebellum with focus on the DN.

Spine Imaging Protocol

3D T_2-weighted images (T_R = 1500 ms, T_E = 120 ms, flip angle = 120°, voxel size = 0.8 mm isotropic, FOV = 256 × 256 mm^2) were acquired to position the voxel for MRS.

To estimate neurochemical alterations, a semi-LASER sequence (T_R = 3000 ms, T_E = 28 ms, averages = 128)[1,2] was used at the level of the cervical vertebrae C4-C5 (volume of interest = 8 × 6 × 30 mm^3). An asymmetric adiabatic radiofrequency pulse (duration = 30 ms) was used to invert metabolite peaks every other shot while maintaining the amplitude and phase of water peak.[3] Only partial water suppression was performed to preserve enough water signal for shot-to-shot frequency and phase correction. Furthermore, two unsuppressed water spectra were acquired for eddy current correction and as a reference for metabolite quantification.[2]

Diffusion data were acquired along 63 directions and interleaved with 7 nondiffusion weighted images. In addition, 5 nondiffusion weighted images with the opposite phase encoding were also acquired for distortion correction. The three Prisma scanners utilized the *syngo* ZOOMit (Siemens Healthineers AG, Erlangen, Germany) echo-planar spin-echo sequence for diffusion data acquisition (T_R = 6700 ms, T_E = 73 ms, flip angle = 90°, voxel size = 0.65 × 0.65 × 3.0 mm, FOV = 130 × 44 mm^2, *b*-values = 550 s/mm^2 and 1000 s/mm^2), as previously described.[4] On the Skyra scanner, for which ZOOMit was not available, diffusion data were acquired using an echo-planar spin-echo sequence with outer-volume suppression pulses to avoid signal contribution from tissues located anterior or posterior to the spine (T_R = 6700

ms, T_E = 80 ms, flip angle = 90°, voxel size = 0.68 × 0.68 × 3.0 mm, FOV = 130 × 44 mm^2, *b* values = 550 s/mm^2 and 1000 s/mm^2).

Data Analysis

The longitudinal pipeline of Freesurfer version 6.0[5] was used on the brain T1 images to achieve a robust brain volumetric analysis, because this approach accounts for interindividual and intraindividual morphological variabilities. This involved creating a template for each participant, to which all their longitudinal brain images were registered and then segmented to extract the volume of subcortical regions including the medulla, pons, midbrain, thalamus, third and fourth ventricles, caudate and putamen. A spatially unbiased atlas template of the cerebellum and brainstem (SUIT) toolbox[6] was used on the brain T1 and T2 images to automatically isolate and segment the cerebellum. The morphology enabled dipole inversion toolbox[7] was used to quantitatively map susceptibility in the combined multi-echo gradient echo images. To extract the DN, we manually defined the bean-shaped structure on the susceptibility-weighted image on four different slices for each side of the dentate (spaced out across the structure). This manually defined mask was used as a constraint in the SUIT toolbox to improve the spatial normalization of the DN to the SUIT template and thus enhance the segmentation of the DN.[8].

The spine section in the brain T_1 images (upper cervical spine C1-C3 was automatically segmented using the Spinal Cord Toolbox (version 4.0.0).[9] A manual labeling of the C2-C3 intervertebral disc was performed to initialize the automatic detection of all the vertebral levels. The cross-sectional area and eccentricity were then computed for the cervical regions C1-C3.

The large residual water peak in the MRS data allowed for an effective shot-to-shot frequency and phase correction using in-house scripts written in MATLAB (MathWorks, Inc., Portola Valley, CA, USA). The unsuppressed water signal was used for eddy current distortion correction, and as an internal reference for metabolite concentrations estimation.

The alternating shots were subtracted to remove the water peak while adding up the metabolite peaks. The metabolites were then quantified using LCModel[9] with a simulated basis-set.[11] The total *N*-acetylaspartate to myo-inositol (tNAA/mIns) ratio was calculated.

Diffusion data from the brain and spine were denoised and Gibbs-ringing artifacts removed using MRtrix3.[12,13] FSL version 6.01 Eddy tool[14] with outliers replacement[15] and slice-to-volume motion model[16] was used to correct eddy currents and movement artifacts. FSL Topup tool[17] was used to correct susceptibility-induced distortion artifacts. The corrected spine diffusion data were fitted to the diffusion tensor imaging (DTI) model using robust estimation of tensors by outliers rejection.[18] The spine DTI metrics were registered to the PAM50 template[19] and mean values were extracted along the cervical vertebrae C2-C6. The corrected brain diffusion data were also fitted to the DTI model using the standard fitting algorithm implemented in FSL[20] on the low *b*-value images (b = 1500 s/mm^2 for Prisma scanner and b = 1000 s/mm^2 for Skyra scanner) to generate the fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity maps. Mean values of those DTI metrics were extracted from the superior and inferior cerebellar peduncles, and the posterior limb of internal capsule. In addition, to properly model complex crossing-fibers configurations present in many white matter areas, we performed fixel-based analysis (FBA)[21] on the corrected multi-shell data to extract the fiber density (FD, intra-axonal volume), fiber cross-section (FC, total area occupied by axons) and a combination of both FD and FC (FDC, fiber density and cross-section).[21] The average response functions of the white matter and cerebrospinal fluid from the baseline data of all participants were used to estimate the fiber orientation distribution (FOD) using the constrained spherical deconvolution approach,[22] and create a template FOD to which all participants' FODs were registered. The FBA metrics were then estimated from the registered FODs. Mean FBA metrics were then extracted from the superior and inferior cerebellar peduncles, posterior limb of internal capsule, corticospinal tract, superior corona radiata, and medial lemniscus.

eReferences

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Post Hoc Analyses

Post hoc statistical analyses included an O'Brien composite variable analysis with change in iron concentration (assessed by QSM), cervical spinal cord tNAA/mIns ratio (assessed by MRS) and cerebellar composite functional scale (CCFS) score as variables. For each individual outcome, patients were ranked according to the improvement between baseline and week 48, and the O'Brien variable was calculated as the sum of ranks for change in iron concentration, tNAA/mIns ratio and CCFS score at week 48. All patients were included (N = 32) and missing values (MRS, n = 8; QSM, n = 6; CCFS, n = 1) were imputed with the value of the median change for all patients at the specific time point. Differences in average ranks between the two treatment groups were determined statistically with a non-parametric rank sum test.

In a post hoc subpopulation analysis, the rate of disease progression at baseline was calculated based on total SARA divided by disease duration. These scores were then plotted relative to a regression line (assuming a SARA score of 0 when disease duration is 0, and an average increase of 1.13 total SARA points per year for this population),[1] to identify faster and slower progressors. To allow comparison of more homogeneous populations, patients in the placebo group were matched with all patients in the leriglitazone group who had similar baseline characteristics in terms of age, disease duration, age at onset, and baseline SARA score. Differences in SARA, Activities of Daily Living, CCFS, QSM, and tNAA/mIns results between groups were then assessed.

CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ON THE EFFECTS OF MIN-102 ON BIOCHEMICAL, IMAGING, NEUROPHYSIOLOGICAL, AND CLINICAL MARKERS IN PATIENTS WITH FRIEDREICH'S ATAXIA

CONFIDENTIAL

Sponsor code: MT-2-03
EudraCT number: 2018-004405-64

Investigational product	MIN-102
Clinical Phase	Phase 2a
Indication to be studied	Friedreich's Ataxia
SPONSOR	Minoryx Therapeutics BE SA Rue Auguste Piccard 48 6041 Gosselies. Belgium
CONTRACT RESEARCH ORGANIZATION	Premier Research S.L.U Camino de la Zarzuela, nº 19, 1º B 28023 Madrid. Spain
PRINCIPAL INVESTIGATOR	
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E-mail:	alexandra.durr@icm-institute.org

Version 4.0, 25 February 2020

This study will be conducted in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and in accordance with local legal and regulatory requirements.

Confidentiality Statement:

AUTHORIZATION OF CLINICAL STUDY PROTOCOL

Sponsor

Minoryx Therapeutics BE SA
Rue Auguste Piccard 48
6041 Gosselies. Belgium

Director
Marc Martinell *Signature: ……* *Date: ……*

Chief Medical Officer (CMO)

Uwe Meya *Signature: ……*
Date: ……

Principal Investigator (PI)

Prof. Alexandra Durr *Signature: ……* *Date: ……*

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Minoryx Therapeutics BE SA.
- Not to implement any changes to the protocol without written agreement from Minoryx Therapeutics BE SA and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study medication, as described in this protocol and any other information provided by Minoryx Therapeutics BE SA including, but not limited to, the current Investigator's Brochure.
- That I am aware of, and will comply with, Good Clinical Practice (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Minoryx Therapeutics BE SA study medication and have been trained on their study-related duties and functions as described in the protocol.

Signature:

Date:

Name (print):

Investigator

Institution name and address (print):

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (See Section 6.1), the principal investigator will send a report within 24 hours of notification to:

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Role	Company / Address
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Drug Supplies Management & Distribution: Drug Study Manufacturers, primary packaging and labelling, final configuration and final release of the clinical supplies.	Laboratorium Sanitatis SL - TECNALIA P.T. Alava – C/ Leonardo Da Vinci, 11 01510 Miñano (Álava) Spain
Home Nursing	Illingworth Research Group Limited St. George's House, 1 St George's Street Macclesfield, Cheshire, SK11 6TG. United Kingdom

SYNOPSIS

Protocol Title

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ON THE EFFECTS OF MIN-102 ON BIOCHEMICAL, IMAGING, NEUROPHYSIOLOGICAL, AND CLINICAL MARKERS IN PATIENTS WITH FRIEDREICH'S ATAXIA

Study codes

Sponsor code: MT-2-03
EudraCT number: 2018-004405-64

Sponsor

Minoryx Therapeutics BE SA, Rue Auguste Piccard 48, 6041 Gosselies, Belgium

Sponsor's Contact: Sílvia Pascual, MSc, Director of Clinical Operations

Study Sites

The study will be conducted at approximately 4 sites in Europe.

Clinical Phase

This is a phase 2a study.

Objectives

Primary Objective

The primary objective of the study is to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on cervical spinal cord area as assessed by morphometric MRI measurements.

Secondary Objectives

The secondary objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change from baseline in the total score of the SARA
- Cervical spinal cord mean, axial and radial diffusivity as assessed by MRI diffusion tensor imaging (DTI)
- Cervical spinal cord tNAA/mIns ratio as assessed by MRS
- MRI quantitative susceptibility mapping (QSM) for iron concentration
- Dentate nuclei volume
- Brain fiber density, fiber cross-section and fiber density and cross-section (FDC) as assessed by fixel-based analyses (FBA)
- Cerebellar Composite Functional Scale (CCFS), composed of 2 functional tests: 9-hole peg test and clicking
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- Fatigue Severity Scale (FSS)
- Activities of daily living (subscale of the Friedreich's Ataxia Rating Scale [FARS])
- Clinician and patient global impression of improvement

- Safety and tolerability of MIN-102 for up to 48 weeks of treatment and 4 weeks after discontinuation by assessment of AEs, vital signs, 12-lead ECG, echocardiogram, clinical laboratory tests, and palatability.

Exploratory Objectives

The exploratory objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change in the pre-treatment versus post-treatment slope of the SARA
- Neurophysiological parameters as assessed by motor evoked potentials (MEP) as an optional assessment
- Biochemical parameters in plasma: adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells and additional panel of biomarkers related to neurodegeneration and neuroinflammation.
- Biochemical parameters in CSF (optional): adiponectin, neurofilament light chain adiponectin, Fatty acid binding protein 4 and additional panel of biomarkers related to neurodegeneration and neuroinflammation
- Volume of further specific brain regions
- DTI parameters, including fractional anisotropy, mean, axial, and radial diffusivity, in specific brain regions

Pharmacokinetic Objectives

- To determine MIN-102 and M3 concentrations in plasma

Study Medication and Subject dosing

Study drugs

MIN-102	:	5-[[4-[2-[5-(1-Hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]-2,4 thiazolidinedione hydrochloride (1:1)
Activity	:	Peroxisome proliferator-activated receptor gamma agonist
Strength	:	15 mg/mL
Dosage form	:	Oral suspension
Placebo	:	Matching study drug visually and by taste
Activity	:	Not applicable
Strength	:	Not applicable
Dosage form	:	Oral suspension
Manufacturer	:	Laboratorium Sanitatis SL P.T. Alava – C/ Leonardo Da Vinci, 11 01510 Miñano (Álava) - Spain Tel.: +34 902 760 000

Subjects will be randomized in a 2:1 ratio to MIN-102 or placebo. Subject will receive an individualized starting dose of MIN-102 or placebo. Subjects will be instructed to take a daily dose of the study treatment at approximately the same time in the morning throughout the entire treatment phase. The administered dose of MIN-102 is intended to achieve a target exposure of

170 µg.hr.mL-1. The dose may be individually adjusted to achieve the target exposure based on pharmacokinetic parameters obtained from the blood samples at the study visits.

Duration of Treatment

Patients will receive MIN-102/placebo for 48 weeks.

Study Population

It is planned to randomize a total of 36 patients who fulfill all the inclusion criteria and any of the exclusion criteria to achieve 30 evaluable patients.

Inclusion Criteria

Only subjects who meet all of the following criteria will be eligible for inclusion in the study:

24. Signed Informed Consent by the subject or parent/legal guardian, and/or consent or assent for minors as required by national laws.
25. Male and female subjects aged ≥12 and ≤60 years, inclusive, with Friedreich's Ataxia confirmed by genetic testing.
26. Total score on SARA of <25.
27. Score on SARA item 1 (gait) ≥2 and ≤6.
28. Male with a potentially fertile partner must be willing to use an acceptable method of contraception for the duration of the study and for 3 months after study drug discontinuation (acceptable methods are: use of a condom with spermicide or use of oral, implantable or injectable contraceptives, or intrauterine devices, or a diaphragm with spermicide or diaphragm with condom) or have had a vasectomy.
29. Female with childbearing potential must be willing to use highly effective contraceptive methods during screening, during the period of drug administration and for 30 days after stopping study drug administration. Highly effective contraception methods include the following:
    - Total abstinence (defined as refraining from heterosexual intercourse during the entire period outlined above).
    - Male or female sterilization.
        - bilateral tubal occlusion
        - vasectomized partner
    - Use of at least one of the following:

      a. Use of oral, injectable, transdermal, intravaginal, or implantable hormonal methods of contraception

        - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral, intravaginal or transdermal.
        - progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable

      b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
30. Female patients of childbearing potential must have a negative serum pregnancy test result within 7 days before first administration of study drug.

Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

31. Age of onset of disease ≥25 years.
32. Left ventricular ejection fraction (LVEF) <55%, on echocardiogram.
33. History of heart failure. Ventricular arrhythmia, supraventricular tachycardia, or having a QTcF time of >480 msec in 3 consecutive ECG recordings taken at least 5 minutes apart.
34. Known intolerance to pioglitazone or other thiazolidinediones.
35. Currently taking or have taken pioglitazone, or other thiazolidinediones, within the past 6 months prior to Screening.
36. Currently participating in or having participated in another interventional clinical study within 2 months prior to Screening.
37. Requiring other prohibited concomitant medication (see Table 4). Note: use of idebenone, coenzyme Q10, antioxidants, riboflavin, thiamine, vitamins C and E is permitted provided the dose has been constant for ≥3 months before Screening and is kept constant during the entire study.
38. Previous or current history of vesical polyps, bladder cell hyperplasia, or bladder cancer.
39. Previous or current history of other cancer, unless surgically resected and without evidence of recurrence for a minimum of 5 years.
40. Clinically significant anemia (i.e. hemoglobin below 110 g/L).
41. Glycated hemoglobin (HbA1c) levels >6.4% and fasting blood glucose levels ≤ 0.9 times the lower limit of normal and ≥ 1.1 times the upper limit of normal.
42. NT-proB-type natriuretic peptide level (NTpro BNP) >125 pg/mL.
43. Abnormal liver enzyme tests for aspartate aminotransferase or alanine aminotransferase of >2 times the upper limit of normal or total bilirubin >1.5 times the upper limit of normal (unless due to Gilbert's syndrome).
44. A positive result on laboratory tests for hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody at screening.
45. Moderate or severe hepatic impairment (groups B and C according to the revised Child-Pugh classification; see Appendix 6.2) [2].
46. Chronic kidney disease (CKD) stages 3a or higher (according to CKD staging by Renal Association with an estimated glomerular filtration rate of <60 ml/min/1.73m^2).
47. Contraindications for MRS/MRI procedure such as subjects with ferromagnetic materials in the body, such as dental braces, spinal rods, aneurysm clips, pacemakers, intraocular metal or cochlear implants.
48. Drug or alcohol abuse in the past 2 years by subject history and/or investigator assessment.
49. Conditions which could modify the absorption of the study drug, such as inflammatory bowel diseases, or stomach or intestinal resection.
50. Inability or unwillingness of the subject or subjects' parents/caregivers to comply with the study procedures.

51. Other medical, neurological, psychiatric, or social conditions that in the investigator's opinion are likely to confound the assessment of safety or efficacy, interfere with study conduct, or unfavorably alter the risk-benefit of subject participation.
52. Pregnant women as confirmed by a positive blood hormonal test.
53. Female patients intending to breast feed a child while taking study drug or have taken study drug within 30 days after administration of the last dose.

Study Overview/Design

Eligible subjects will be randomized to treatment for 48 weeks with MIN-102 or placebo in a 2:1 ratio after obtaining written informed consent from the subject or, if the subject is a minor, obtaining written informed consent from a parent/legal guardian and written assent from the subject, completion of all screening evaluations within 28 days (4 weeks), and confirmation that the subject has met all inclusion criteria and none of the exclusion criteria.

Motor Evoked Potentials and cerebrospinal fluid sampling are optional and require separate informed consent and assent.

The Screening visit (V-1) occurs after written informed consent is obtained. After the Screening visit, eligible subjects fulfilling all the inclusion and none of the exclusion criteria will be scheduled for a Baseline visit (V0) within a maximum of 28 days after the Screening visit (V-1) and will be randomized to receive an individualized starting dose of MIN-102 or placebo. Subjects will be instructed to take a daily dose of the study treatment at approximately the same time in the morning throughout the entire treatment phase. The administered dose of MIN-102 is intended to achieve a target exposure of 170 $\mu g \cdot hr \cdot mL^{-1}$.

In addition to the Screening visit (V-1) and Baseline visit (V0), subjects will be evaluated at two interim safety visits (ISVs) occurring 2 and 8 weeks after V0 (ISV1 and ISV2), and at 4 (V1), 12 (V2), 24 (V3), 36 (V4), and 48 (V5) weeks after V0.

ISV1 and ISV2 may occur at home, all other visits will be performed on-site. The home visits will be performed by an accredited nurse who is certified in Good Clinical Practice (GCP). Results of all scheduled assessments will be made available to the investigator as soon as possible.

Post-baseline evaluations will consist of assessments for safety and tolerability and blood sampling for plasma levels of MIN-102 at all scheduled on-site visits (except for ISV1 and ISV2), imaging evaluations at V3 and V5, assessment of biochemical markers in plasma at V2, V3, V5, and the follow-up visit (FUV; 4 weeks after last dose of study drug), assessment of biochemical markers in CSF at V3 and V5 (optional), evaluations of clinical status on SARA, global clinical rating scales, MEP, and patient questionnaires at V3 and V5. All assessments for safety, tolerability, and biochemical markers in plasma will also be performed at premature discontinuation.

There will also be regularly scheduled phone calls to the subjects at 6, 10, 16, 20, 28, 32, 40, and 44 weeks after V0. During these calls, the site will ask the subject for changes in concomitant medications and AEs, in particular for symptoms possibly indicative of cardiac failure.

An individualized dose based on PBPK will be chosen to yield a geometric mean AUC_t of approximately 170 µg•hr/mL. Blood sampling to determine MIN-102 plasma concentrations will occur before the first dose, and then at each scheduled visit (except ISV1 and ISV2) immediately before each daily dose. The observed plasma concentrations of MIN-102 at V1 will be used to guide dose adjustments. After a potential dose adjustment following PK results from V1, no further dose adjustments are allowed, except for dose reductions to manage safety or tolerability issues (see sections 3.4.3 and 3.4.4 for further details)

Individual downward adjustments of the dose at any time point after V0 may be implemented by the investigator for safety/tolerability reasons; however, the minimum permitted dose in terms of corresponding volume rounded to the nearest 0.5 mL will be individually calculated for each subject to achieve a plasma exposure of ≥100 µg•hr/mL.

A FUV will occur 4 weeks after last dose of study drug.

Planned Study Timelines:

Start clinical phase:	April 2019
End clinical phase:	September 2020
Database lock:	November 2020
Top Line Results:	December 2020
Final report complete:	February 2021

Table 1: Flow Chart of Study Procedures

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Informed consent[11]	X														
Assignment of subject identification number	X														
Inclusion & exclusion criteria	X	X[2]													
Medical history/concomitant disease	X	X[2]													
Demographics	X														
Previous medication	X	X[2]													
Physical examination	X		X[7]	X[7]		X[7]		X		X		X		X	X
Vital signs (height, body weight, blood pressure, pulse rate, temperature)[3]	X	X	X	X		X		X		X		X		X	X
Echocardiogram	X			X				X		X		X		X	X

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody	X														
Hba1c	X													X	X
Pregnancy test[12]	X	X		X		X		X	X	X	X	X	X	X	X
Laboratory safety tests (haematology, blood chemistry, prothrombin time, NTpro BNP, urinalysis including cytology)[4]	X	X		X				X		X		X		X	X
Randomization[5]		X													
Biomarker blood sampling[6]		X						X		X				X	
Biomarker CSF sampling (optional)[6]		X								X				X	
Blood sampling (MIN-102 and M3 levels)[6]		X		X				X		X		X		X	
Subject diary review			X	X		X		X		X		X		X	

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Study drug and study diary dispensation		X						X		X		X			
Study drug accountability								X		X		X		X	
Palatability assessment[10]		X		X				X		X		X			
12-lead ECG (in triplicate)	X	X[8]		X[8]				X[8]		X[8]		X[8]		X	X
SARA	X	X								X				X	
CCFS		X								X				X	
MRI/MRS		X								X				X	
MEP (optional)		X								X				X	
CGI-S		X								X				X	
CGI-I										X				X	
PGI-I										X				X	
FSS		X								X				X	
EQ-5D-5L		X								X				X	
Activities of Daily Living subscale of FARS		X								X				X	

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Adverse event recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

NTpro BNP = NT-proB-type natriuretic peptide; CCFS = cerebellar composite functional scale; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; CSF = cerebrospinal fluid; ECG = electrocardiogram; EOT=End of treatment; EQ-5D-5L = European Quality of Life 5 Dimensions; FARS = Friedreich's Ataxia Rating Scale FSS = Fatigue Severity Scale; FUV = follow up visit; ISV = interim safety visit; MEP = motor evoked potentials; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PGI-I = Patient Global Impression – Improvement; SARA = Scale for the Assessment and Rating of Ataxia; V = visit

[1] To be performed for all subjects, including those who discontinue prematurely
[2] Confirmation of screening information
[3] All assessments at V0 and later are performed immediately prior to study medication administration. Temperature measurements will only be performed at V0, V5 and FUV, and height only at screening (V-1).
[4] Samples are collected pre-dose at the same time as pharmacokinetic samples, in the morning under fasted conditions.
[5] After all entry criteria are confirmed
[6] Pre-dose
[7] Only examination for peripheral edema
[8] At the Baseline visit (V0) ECGs will be recorded pre-dose and approximately 3 hours post-dose. At visits from V1-V4 they will be recorded at approximately 3 hours post-dose.
[9] Clinic or home visit
[10] Immediately after administration of daily dose
[11] If subject becomes 18 years old during the study, signature of the adult ICF will be required.
[12] Female patients of childbearing potential will have a serum pregnancy test within 7 days before the first study drug administration. If the Screening Visit has been performed > 7 days before the Baseline Visit, a home nurse visit may be scheduled to perform the serum test. At Screening a serum pregnancy test will be performed. At Baseline and FUV a urine and serum pregnancy test will be performed. All the remaining visits (monthly) urine pregnancy test will be

performed, and a positive result will be confirmed by a serum test as soon as possible. If pregnancy is suspected during the study, an unscheduled serum pregnancy test will be performed as soon as possible.

[13] Any definitive discontinuation of the drug must be considered EOT, either by the end of the study at Visit 5 or by premature discontinuation of study drug prior to Visit 5. In both cases, the assessments and procedures scheduled for V5 have to be performed.

EOT visit must be performed as soon as possible after study drug discontinuation. If an MRI has been performed within three months prior to discontinuation, no additional MRI has to be performed. Same applies to SARA, CCFS, MEP (in case the patient has consented), CGI-S, CGI-I, PGI-I, FSS, EQ-5D-5L, and activities of daily living subscale of FARS. If these assessments have been performed within the three months prior to discontinuation, no additional assessment will be performed.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALD	adrenoleukodystrophy
ALT	alanine aminotransferase
AMN	adrenomyeloneuropathy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	AUC from time 0 extrapolated to infinity
AUC_t	AUC from time 0 to end of dosing period
NTpro BNP	NT-proB-type natriuretic peptide
CCFS	Cerebellar Composite Functional Scale
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CSF	cerebrospinal fluid
CST	corticospinal tract
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DTI	diffusion tensor imaging
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5 Dimensions
FA	fractional anisotropy
FABP4	fatty acid binding protein 4
FARS	Friedreich's Ataxia Rating Scale
FBA	fixel-based analyses
FC	fiber cross-section
FDA	Food and Drug Administration
FD	fiber Density
FDC	fiber density and cross-section
FE	food effect

Abbreviation	Definition
FRDA	Friedreich's ataxia
FSS	Fatigue Severity Scale
FUV	follow-up visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	glycated hemoglobin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISV	interim safety visit
KIKO	frataxin knock-in/knockout mice
LLOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
M3	metabolite no. 3
MAD	multiple ascending dose
MEP	motor evoked potentials
mIns	myo-inositol
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	N-acetylaspartate
NOAEL	no-observed-adverse-effect level
NRF1	nuclear respiratory factor 1
PBPK	physiologically based pharmacokinetic modeling
PGC-1α	peroxisome proliferator-activated receptor γ coactivator
PGI-I	Patient Global Impression – Improvement
PK	pharmacokinetic
PP	per-protocol
PPB	parts per billion
PPARγ	peroxisome proliferator-activated receptor γ
PT	preferred term
QSM	quantitative susceptability mapping
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
SARA	Scale for the Assessment and Rating of Ataxia
SD	standard deviation

Abbreviation	**Definition**
SOC	system organ class
SUSAR	suspected unexpected serious adverse drug reactions
$t_{½}$	half-life
TFAM	mitochondrial transcription factor A
tNAA	total N-acetylaspartate
tNAA/mIns	total N-acetylaspartate/myo-inositol
ULN	upper limit of normal

1. INTRODUCTION

1.1. Overview of Friedreich's Ataxia

Friedreich's ataxia (FRDA) is an autosomal recessive neurodegenerative disorder characterized by progressive spinocerebellar ataxia, and is associated with cardiomyopathy, scoliosis, decreased glucose tolerance, and diabetes. There are currently no approved treatments for FRDA; current therapy focuses on management of symptoms of the disease. Most cases of FRDA are due to a pathogenic homozygous GAA expansion within the first intron of the FXN gene, the gene that encodes a protein called frataxin that is typically found in high quantities in cardiomyocytes and dorsal spinal column neurons. Frataxin localizes to the mitochondria and is involved in the assembly of iron-sulfur clusters [3]. The GAA expansion results in reduced frataxin transcription. Reduced frataxin transcription leads to abnormal mitochondrial iron accumulation and an increase in oxidative stress resulting in changes to mitochondrial function. Frataxin deficiency is also associated with changes in downstream gene expression, including those genes that may impact the FRDA clinical phenotype. Coppola et al. investigated gene expression phenotypes in lymphocytes from FRDA patients, heterozygous carriers, and normal controls and identified a set of downregulated genes associated with clinical disease status that distinguishes FRDA patients from carriers and controls [4]. One of the most dysregulated genes is APTX that encodes aprataxin, which is essential for deoxyribonucleic acid (DNA) repair after oxidative stress damage.

Friedreich's ataxia results in various changes in clinical, neuroimaging, neurophysiological and biochemical parameters. FRDA is a progressive disorder with the first symptoms including gait instability with imbalance and a risk of falls and dysarthria. Symptoms to follow include loss of fine motor skills, dysmetria, intention tremor, and dysphagia. Typically within 10 to 15 years, FRDA patients cannot walk, sit, or stand anymore without support [5]. However, there is considerable variability in the speed of disease progression. In a large cohort of 592 patients with genetically confirmed FRDA that were recruited through the European Friedreich's Ataxia Consortium for Translational Studies, age of onset was shown to be a strong predictor of the speed of progression, with young-onset patients (age ≤ 14 years) progressing the fastest, and late-onset patients (age ≥ 25 years) progressing the slowest [6]. The age group of > 14 and < 25 years showed an intermediate speed of progression.

Rate of decline with FRDA is also associated with various neurophysiological parameters, including motor-evoked potentials. Several publications confirm cerebellar and pyramidal path involvement during the course of clinical decline in FRDA with decreased central motor conduction time and amplitude and increased threshold [7-9]. These changes correlate with disease duration, clinical decline, and number of GAA repeats.

MIN-102, a metabolite of pioglitazone, is a selective peroxisome proliferator-activated receptor γ (PPARγ) agonist that stimulates PGC-1α expression in neurons and may be a desirable therapy for treating FRDA [10]. Pioglitazone, an approved treatment for type II diabetes, was tested in clinical studies of amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Friedreich's ataxia. Studies performed to date have not shown clinical benefit; however, the pioglitazone doses studied were in the range used to manage diabetes, for which the circulating levels achieved were 2 to 4 times lower than those with activity in preclinical models of these conditions. While efficacious results have not been observed in clinical trials, there is published data supporting the use of PPARγ agonists for the treatment of FRDA based on studies performed in tissues from animals (KIKO mouse model), cellular models of frataxin deficiency, and in cells from FRDA patients. These studies showed a correlation between a decrease in frataxin and downregulation of genes that impact mitochondrial function, lipid metabolism, cell cycle, and DNA repair, consistent with FRDA's known pathophysiology. Peroxisome

proliferator-activated receptor γ coactivators PGC-1α and superoxide dismutase 2 are examples of genes downregulated in FRDA models, highlighting an important role of mitochondrial dysfunction and oxidative stress in the pathogenesis of this disease [11-15]. MIN-102 is the main active metabolite of pioglitazone and contributes a majority of the pharmacological activity of administered pioglitazone. MIN-102 is suggested to show greater efficacy in neuroinflammatory disease than pioglitazone, as metabolic conversion is not needed to produce the active agent. It is also suggested that MIN-102 may be associated with a better safety profile than pioglitazone due to having a simpler metabolic profile than pioglitazone.

Various parameters have been used to assess progression and severity of FRDA. Linear regression analyses of disease duration reported at baseline versus the scores of the Scale for the Assessment and Rating of Ataxia (SARA) generated estimates of annual rates of decline. Early-onset, intermediate-onset and late-onset showed a predicted decline of 1.17, 1.04 and 0.56 points per year on SARA, respectively. Using observed follow-up rates after 2 years of observation for "typical-onset" patients aged ≤ 24 years, the rate of annual decline was calculated as 0.75 points per year on SARA [16].

Rates of disease progression can also be calculated using various imaging parameters. Henry et al. are following a cohort of patients with FRDA longitudinally with diffusion-tensor imaging (DTI) of the spinal cord, magnetic resonance spectroscopy (MRS), and structural magnetic resonance imaging (MRI) [17,18]. Magnetic resonance spectroscopy showed that the total N-acetylaspartate/myo-inositol (tNAA/mIns) ratio decreased by 17% on average over 24 months. Diffusion-tensor imaging showed a 26% increase in mean diffusivity and an 18% decrease in spinal cord area over this period. Fractional anisotropy, also assessed by DTI, increased from baseline during the first 12 months. This increase was interpreted as a compensatory mechanism in the affected regions of the spinal cord. Additional follow-up after 24 months showed that the increase in fractional anisotropy noted at the 12-month time point was no longer present and now presented as a decrease from baseline. Morphometry, assessed by structural MRI, showed reduced spinal cord area (-28%) and increased eccentricity (+13%), consistent with atrophy of dorsal and lateral columns of the spinal cord. These results indicate that imaging is able to detect functional and structural changes in the spine over a relatively short period of time.

Morphometric changes in MRI parameters in FRDA are associated with measures of clinical decline. Dogan et al. demonstrated that cross-sectional area, volume, and eccentricity differ significantly between patients with FRDA and normal volunteers at almost all levels of the cervical and thoracic spinal cord, the medulla, and the pons [19]. Regression analysis showed that various MRI measures predicted clinical changes on SARA, Inventory of Non-Ataxia Signs, and activities of daily living. Thus, morphometric parameters may be relevant correlates of clinical status and decline.

Several potential biomarkers have been identified that may aid in the assessment of FRDA. Neurofilament light chain, one of the scaffolding proteins of the neural cytoskeleton, was recently identified as a promising biomarker of neurodegeneration [20]. Neurofilament light chain is increased in plasma and cerebrospinal fluid (CSF) of patients with various neurodegenerative disorders, including Parkinson's dementia [21], amyotrophic lateral sclerosis [22], fronto-temporal dementia [23], and Alzheimer's disease [24]. Plasma concentrations of neurofilament light chain were significantly increased in patients with premanifest Huntington's disease compared to healthy controls and correlated with various measures of cognition and morphometric brain changes. Neurofilament light chain plasma concentration was also associated with subsequent onset of clinical symptoms of Huntington's disease during a 3-year follow-up period [25]. Also, neurofilament light chain levels in CSF were associated with lower diffusion tensor imaging fractional anisotropy and increased radial diffusivity in the corticospinal tract (CST) of

amyotrophic lateral sclerosis patients indicating the potential for combining neurochemical and neuroimaging-based biomarkers in the assessment of neurological disease [26](Menke et al., 2015). Recently, a study investigating plasma markers of neurodegeneration, including neurofilament light chain, in FRDA showed that mean plasma levels were significantly higher in FRDA patients than in controls ($p<0.001$), potentially reflecting ongoing neuronal degeneration [27]. Dysregulation of the PPAR gamma/PGC-1α pathway was reported in tissues from the KIKO mouse model of FRDA, frataxin deficient cell models and fibroblasts and lymphoblasts from FRDA patients (Coppola et al., 2009; Marmolino et al., 2010). Additionally, PGC-1α levels correlate with frataxin levels in neural precursor cells from mouse models and in cells from patients with FRDA [11]. Similarly, the levels of the PGC-1α downstream effectors, nuclear respiratory factor 1 (Nrf1) and mitochondrial transcription factor A (Tfam), are significantly decreased in the KIKO mouse model, suggesting early impaired cerebellar mitochondrial biogenesis [12] and downregulation of these markers was also demonstrated in FRDA patient fibroblasts and correlated with frataxin expression (Jasoliya et al., 2017). These findings suggest markers of neurodegeneration and mitochondrial biogenesis may be used in assessment of FRDA.

This study with MIN-102 will investigate whether treatment with MIN-102 is able to influence clinical, neurophysiological, and imaging parameters, as well as various peripheral and central nervous system biochemical markers related to mitochondrial dysfunction in subjects with FRDA, over a period of 48 weeks in a double-blind, placebo-controlled design.

1.2. Nonclinical Experience

1.2.1. Nonclinical Pharmacology

MIN-102, through its PPARγ activity, induces neuroprotective and restorative effects in several preclinical models of neurodegenerative disease with motor dysfunction (single Abcd1- and double Abcd1^{-}/Abcd2$^{-/-}$ knockout mice) and neuroinflammatory processes [28-31].

MIN-102,was able to protect motor neurons and astrocytes from very long chain fatty acid-induced toxicity, promote a dose-dependent improvement in disability score in mice with experimental autoimmune encephalitis, and restore mitochondrial expression of genes associated with biogenesis, reduced oxidative damage, and reversed proinflammatory status in rat spinal cord tissue [28]. Experiments supporting the treatment of FRDA with MIN-102 show that MIN-102 increases survival, decreases neurite degeneration, and restores membrane potential of frataxin-deficient dorsal root ganglion neurons. In addition, MIN-102 does not affect mitochondrial morphology, but significantly reduces lipid droplets in frataxin-deficient cardiomyocytes resulting in increased fatty acid utilization and restored energy production [28].

Beneficial effects of pioglitazone, MIN-102, and other PPARγ analogues in preclinical models of neuroinflammation were associated with direct stimulation of PPARγ in microglia and neurons and reduction of the neuroinflammatory response and oxidative stress [29,30].

1.2.2. Nonclinical Pharmacokinetics

MIN-102 is the main pioglitazone metabolite in species tested in toxicology studies. MIN-102 accounts for approximately 18% of pioglitazone metabolites in rats. In dogs MIN-102 has an area under the concentration-time curve (AUC) that is 2.7 times greater than that of pioglitazone, and in humans MIN-102 has an AUC that is 2 to 3 times greater than that of pioglitazone [28]. Therefore, these species are significantly exposed to MIN-102 during pioglitazone treatment.

MIN-102 has a simpler metabolic profile than pioglitazone: MIN-102 primarily metabolizes to M3 and both compounds are excreted; pioglitazone is metabolized to 6 different metabolites. After pioglitazone dosing in human subjects, exposure to M4 (MIN-102) is approximately 2 times higher than the parent compound, with both agents having a similar contribution to efficacy.

Various preclinical studies have shown that MIN-102 has lower cytochrome P450 inhibition/induction activity than pioglitazone [28], and is therefore likely to have a lower tendency to interact with other drugs.

1.2.3. Nonclinical Safety

MIN-102 is a well-characterized metabolite of pioglitazone (described as M4 in pioglitazone studies). A reduced toxicology assessment strategy was agreed with the European Medicines Agency (EMEA/H/SA/2862/1/2014/SME/III) based on the understanding that both animals and subjects have been extensively exposed to study drug during pioglitazone treatment. Safety pharmacology for MIN-102 has been evaluated by considering pioglitazone literature data and MIN-102 stand-alone studies.

It is not expected that new safety findings will arise from MIN-102 studies compared with results from prior pioglitazone experience. However, as subjects will be exposed to higher levels of MIN-102 than with pioglitazone, a complete toxicology program is being conducted. Details on the safety profile of pioglitazone can be found in the summary of product characteristics for pioglitazone [32].

A 28-day repeat-dose toxicity study comparing MIN-102 with pioglitazone has been performed in adult rats [28]. The no-observed-adverse-effect levels (NOAELs) were 14.5 mg/kg and 25 mg/kg for pioglitazone and MIN-102, respectively. At the NOAEL for MIN-102, the $AUC_{(0-24h)}$ at steady state was 226 µg•hr/mL for males and 250 µg•hr/mL in females. Similar results were observed in adult male rats in a 13-week repeat dose toxicity; NOAELs for MIN-102 and pioglitazone were not determined for female rats in this study due to changes in the reproductive tract. A 6-month repeat dose toxicity study in adult rats showed a lower NOAEL for MIN-102 than was observed in the 13-week or 28-day study (12.5 mg/kg; AUC_t = 108 µg•hr/mL for males and 146 µg•hr/mL for females); reductions in NOAEL levels over time are as expected for PPARγ agonists. At higher doses in the 6-month study, a clear effect of MIN-102 on red cell parameters suggestive of hemodilution and increased heart weights (~20% greater than control group) not accompanied by microscopic cardiac changes were the most salient findings and suggested that the death of several rats at higher doses may be attributed to heart failure, a known PPARγ agonist safety concern in toxicology species and humans. Similar results were observed in a 10-week toxicity study in juvenile rats, where the NOAEL based on AUC_t was approximately 168 µg•hr/mL for males and 240 µg•hr/mL for females.

All MIN-102-related findings in the repeated-dose toxicity studies in adult rats (4, 13 and 26 weeks), in juvenile rats (10 weeks) and adult dogs (3 and 9 months) were similar to findings observed in rats and dogs administered pioglitazone. No unexpected new toxicities were observed in rats and dogs administered MIN-102. Thus, higher doses of both compounds did not show differences in toxicology findings, which were consistent with the safety profile of other PPARγ agonists. Additionally, no decreases in plasma glucose levels were observed. Therefore, the human target exposure of 170 µg•hr/mL (±20%) is expected to confer efficacy without exposing subjects to undue risk.

In vitro genotoxicity studies with MIN-102 demonstrated lack of genotoxic potential [28].

No relevant toxicity findings have been identified for respiratory, central nervous, or cardiovascular systems in animal models [28].

1.3. Clinical Experience

1.3.1. Phase 1 Study MT-1-01

This was a phase 1, randomized, double-blind, placebo-controlled, single-center clinical study in healthy male volunteers, divided into 3 parts: a single ascending dose (SAD) part A with 3 dose levels (30, 90, and 270 mg MIN-102) followed by a food effect (FE) part (SAD/FE part); a multiple ascending dose (MAD) part B in a double-blind, parallel design with 2 dose levels (135 mg or 270 mg MIN-102; once daily for 8 days); and an open-label MAD part C in a parallel design with 2 dose levels (135 mg or 270 mg MIN-102; once daily for 8 days) including CSF collection. Part A of the study comprised the first administration of MIN-102 in man.

A total of 33 subjects were included in the study: 9 subjects aged between 21 and 50 years in Part A, 18 subjects aged between 19 and 54 years in Parts B, and 6 subjects aged between 26 and 51 years in Part C. Of the 24 subjects in Parts B and C, 12 subjects received MIN-102 in Part B and 6 subjects in Part C. Six subjects in Part B were randomized to placebo. However, due to a dispensing error, 1 subject in Part B who was randomized to placebo received MIN-102 during the second half of the dosing period, and 1 subject who was randomized to MIN-102 received placebo during the second part of the dosing period. These two subjects were included in the safety analyses but were excluded from pharmacokinetic evaluations. One subject discontinued during the course of the study (Part A) for personal reasons and 32 subjects completed the study.

1.3.1.1. Safety

There were no serious adverse events (SAEs) reported in study MT-1-01. All treatment-emergent adverse events were of mild severity and resolved completely. No clinically significant changes occurred in safety laboratory values, electrocardiograms (ECGs), or vital signs.

1.3.1.2. Pharmacokinetics

1.3.1.2.1. Plasma Concentrations

During the SAD part of the study, the highest geometric mean MIN-102 concentrations were observed between 0.25 and 2.5 hours post-dose and increased proportionally with dose. During the MAD part of the study, maximum MIN-102 concentrations after the first dose were reached after 0.25 to 4 hours for 135 mg MIN-102 and between 2.5 and 8 hours for 270 mg MIN-102. Similar plasma concentration-time profiles were observed on Day 8; however, the maximum concentrations of MIN-102 were approximately 1.7 times higher than on Day 1 (135 mg MIN-102, relative C_{max} 1.73, relative AUC 1.70; 270 mg MIN-102, relative C_{max} 1.72, relative AUC 1.81). The observed plasma half-life ($t_{½}$) of approximately 20 to 23 hours (135 mg MIN-102, $t_{½}$ = 20.5 hours; 270 mg MIN-102, $t_{½}$ = 22.5 hours) allows once-daily dosing in humans.

The mean AUC from time -0 extrapolated to infinity (AUC_{∞}) of 165 µg•hr/mL (standard deviation [SD] 61 µg•hr/mL) for the first 135 mg dose was not significantly different to the AUC_t of 152 µg•hr/mL (SD 28 µg•hr/mL) seen on Day 8. Likewise, the mean minimum plasma concentration (C_{min}) at steady state (4153 ng/mL) projected from the first 135 mg dose was not significantly different from the actual mean at Day 8 (C_{min} 4097 ng/mL, [SD 957 ng/mL]). These data showed that C_{min} and AUC_t are linearly correlated.

Consumption of a standard high-fat breakfast after oral administration of MIN 102 resulted in a clear delay in MIN-102 uptake with maximum plasma concentrations (C_{max}) of MIN-102 reached after 3 to 6 hours; however, the extent of exposure (AUC) was essentially not different from the fasting state.

1.3.1.2.2. Physiologically Based Pharmacokinetics Modeling

Physiologically based pharmacokinetic modeling (PBPK) for MIN-102 that incorporates CYP3A4 and CYP2C8-mediated metabolism as well as biliary clearance derived from in-vitro data was developed by Certara using the Simcyp software [33]. During model development, the single-ascending dose (SAD) data were used as the model training dataset and the multiple-ascending dose (MAD) data were used as the model verification dataset. The findings showed that CYP induction was low and insignificant. The final MIN-102 model was prospectively applied to estimate an appropriate starting dose for pediatric clinical evaluation. The default Simcyp ontogeny functions for CYP3A4 and CYP2C8 as well as literature ontogeny functions [34] were applied in separate simulations. Allometric scaling was also applied to scale doses based on body size and was compared to the PBPK-derived doses. Since application of the Simcyp default ontogeny versus the Upreti ontogeny functions did not show significant differences in the projected pediatric doses, the Upreti ontogeny functions were selected for calculating the starting doses.

1.3.1.3. Cerebral Spinal Fluid Concentrations

No quantifiable MIN-102 was detected in pre-dose CSF samples. Geometric mean concentrations of MIN-102 were 188 ng/mL (range 158 ng/mL to 218 ng/mL) 4 hours after the last dose of 135 mg MIN-102 on Day 8, and 332 ng/mL (range 287 mg/mL to 376 ng/mL) after 270 mg MIN-102. Concentrations of MIN-102 in CSF seem to correlate with the plasma C_{max} and AUC for MIN-102.

1.3.1.4. MIN-102 in Urine

Total excretion of free MIN-102 did not increase above 0.4% of the administered dose over the 48-hour collection period (range 0.1 to 0.4%) at any dose level and did not appear to vary with dose, but varied between subjects. Consumption of breakfast did not change the amount of MIN-102 excreted.

1.3.1.5. Pharmacodynamic Effects of MIN-102 in Plasma

Mean plasma concentrations of adiponectin, an indicator of PPARγ receptor engagement, showed a clear increase from Day 1 to Day 8. Adiponectin increased from 4,532 ng/mL at baseline (Day 1 pre-dose) to 13,461 ng/mL (Day 8 pre-dose) after daily dosing with 135 mg MIN-102 and from 5,014 ng/mL at baseline to 21,738 ng/mL pre-dose on Day 8 after daily dosing with 270 mg MIN-102. No change in adiponectin concentrations was observed after 8 days of placebo dosing. Other analytes, including fatty acid binding protein and interferon gamma, showed less variability in various directions, in both the MIN-102 and placebo groups.

1.3.2. Phase 2/3 Study MT-2-01

This is an ongoing phase 2/3, randomized, double-blind, placebo-controlled, multinational, multicenter study with open-label treatment extension to address the effect of MIN-102 on the progression of adrenomyeloneuropathy (AMN) in adult male subjects with X-linked ALD. This study is a 2-part study with enrollment for Part 1 in the U.S. and Europe. Part 1 is the double-blind part of the study; Part 2 is the open-label treatment extension. As of [November 14th, 2018], 111 male subjects of a total anticipated 117 subjects have been randomized to MIN-102 or placebo in a 2:1 ratio and will receive treatment for 96-weeks. This is an exposure-controlled study where subjects receive an individualized

daily dose to achieve a target exposure (AUC) of 200 µg•hr/mL. To date, no Serious Adverse Events (SAE) related to MIN-102 or Suspected Unexpected Serious Adverse Drug Reactions (SUSAR) have been observed in patients treated for up to 11 months. A common adverse event reported in the phase 2/3 study is water retention with weight gain and peripheral edema.

1.4. Study Rationale

MIN-102 is a selective PPARγ agonist that stimulates PGC-1α expression in neurons and may be a desirable therapy for treating FRDA [10]. Currently, there are no approved treatments for FRDA. Most cases of FRDA are due to a pathogenic homozygous GAA expansion within the first intron of the FXN gene, the gene that encodes frataxin that is typically found in high quantities in cardiomyocytes and dorsal spinal column neurons. The GAA expansion results in reduced frataxin transcription that leads to changes in mitochondrial function. FRDA is a progressive disorder with the first symptoms including gait instability with imbalance and a risk of falls and dysarthria. Symptoms to follow include loss of fine motor skills, dysmetria, intention tremor, and dysphagia. Typically within 10 to 15 years, FRDA patients cannot walk, sit, or stand anymore without support [5]. Therefore, there is a high unmet medical need for a treatment that prevents or delays onset of clinical symptoms of FRDA.

Published data supporting the use of PPAR gamma agonists for the treatment of FRDA is based mostly on studies performed in tissues from animal (KIKO mouse model), cellular models of frataxin deficiency, and in cells from FRDA patients. These studies showed a dysregulation of the PPAR gamma/PGC-1 alpha pathway, suggesting that this is a general downstream effector of frataxin deficiency (Coppola et al., 2009; Lin et al., 2017; Marmolino and Acquaviva, 2009; Marmolino et al., 2009, 2010). Additionally, PGC-1 alpha levels were shown to be correlated with frataxin levels in neural precursor cells from mouse models and in cells from patients with FRDA (Coppola et al., 2009).

Treatment with Pioglitazone in vivo in the KIKO mouse model (25mg/Kg/day for 1 month) increased the expression of PGC-1 alpha and SOD2 in the cerebellum and spinal cord (Marmolino et al., 2010) supporting the potential therapeutic use of PPAR gamma agonists for FRDA. Increase of PGC-1 alpha and SOD-2 mRNA and protein levels were also observed in primary fibroblasts from FRDA patients after incubation with 10 microM Pioglitazone at 24, 48, 72 and 96 hours (Marmolino et al., 2010) were increased.

Internal preclinical studies showed that MIN-102promotes a functional recovery of frataxin-deficient neurons and cardiomyocytes in vitro and shows a trend to reverse several biochemical and microstructural changes assessed by MRS and MRI in vivo.

Altogether, published preclinical data with pioglitazone in in vitro and in vivo models of FRDA together with Minoryx results support the efficacy of MIN-102 and its development for the treatment of FRDA.

This study will provide an assessment of the effects of MIN-102 on biochemical, imaging, neurophysiological, and clinical markers in subjects with FRDA.

The study will include male and female patients, aged 12 years and above. It is important to investigate MIN-102 also in children and adolescents below 18 years. Average age of onset was found to be between 12 and 16 years, depending on the participating site, in the largest non-interventional longitudinal study in Europe conducted by EFACTS (European Friedreich's Ataxia Consortium for Translational Studies) and published by Reetz al. 2015. Thus, if the cut-off age for inclusion were at 18 years, it would exclude a considerable segment of the patient population since they may have already progressed too far to be eligible. Patients with age of onset of 14 years or lower show the fastest rate of disease progression

(Reetz et al. 2015). The disease affects male and female patients almost equally, with a slightly higher proportion of female patients according to the EFACTS longitudinal data. Therefore, female patients will have to be recruited as well to adequately reflect the disease prevalence by gender. For female patients of childbearing potential, highly effective measures of contraception are required (for details see section 3.3).

The MIN-102 dose regimen for the study is selected based on nonclinical toxicology, the pharmacokinetic (PK) data from the phase 1 study (MT-1-01) in healthy adult males, and on physiologically based PK modeling (PBPK). In a toxicity study in rats for 28 days, the NOAEL was determined to be approximately 226 µg•hr/mL for males and 250 µg•hr/mL in females. A similar NOAEL in males (239 µg•hr/mL) was observed in a 13-week toxicity study. A 6-month toxicity study in adult rats revealed a lower NOAEL in both males and females (108 µg•hr/mL and 146 µg•hr/mL, respectively), as expected for PPARγ agonists (NOAEL levels decrease over time with PPARγ agonists).

In the phase 1 study MT-1-01, the MIN-102 plasma levels increased linearly with dose and there was no change in clearance with either dose or time. The AUC_t was 152 µg•hr/mL (SD 28 µg•hr/mL) after MIN-102 135 mg once daily dosing for 8 days. Additionally, there were no SAEs reported and all adverse events (AEs) were mild to moderate in severity in study MT-1-01.

An individualized dose based on PBPK will be chosen to yield a geometric mean AUC_t of approximately 170 µg•hr/mL (±20%, an appropriate dose level given the risk of volume overload and ventricular failure in patients with FRDA). Blood sampling to determine MIN-102 plasma concentrations will occur immediately before the first dose, and then at each scheduled office visit immediately before each daily dose. The observed plasma concentrations of MIN-102 will be used to guide dose adjustments. Due to both, nonclinical and clinical observations, subjects will be monitored for edema and potential cardiovascular risks throughout the study. Additional discussion of the rationale for dosing is provided in Sections 3.4.3 and 3.4.4.

1.5. Risk–Benefit Assessment

Preclinical data indicate that MIN-102 may be effective at protecting neuronal tissue from frataxin deficiency and modulating the associated mitochondrial dysfunction processes and oxidative stress associated with progression of FRDA.

The adverse effects of PPARγ agonists are well characterized and agents of this pharmacological class share a common toxicity profile. Pharmacokinetic and pharmacodynamic characteristics for MIN 102 discard any potential association with a novel safety profile compared with pioglitazone; thus, novel toxic effects are not expected given the substantial level of clinical exposure to MIN-102 in patients treated with pioglitazone for type II diabetes. Based on results from toxicology studies performed to date, potential adverse events that can be anticipated from human exposure to MIN-102 are those observed in compounds with PPARγ agonist activity including pioglitazone and from the procedures performed during the course of the study. A special attention will be given to cardiovascular assessments due to the known cardiac involvement in FRDA patients and the possibility for water retention with MIN-102.

Biomarker results in healthy volunteers reveal a marked and dose-dependent increase in adiponectin levels indicative of a significant increase in PPARγ receptor engagement, which can be achieved at doses that are safe and well tolerated.

Physiologically-based pharmacokinetic (PBPK) modeling for MIN-102 was developed to allow a reliable estimate of the appropriate starting dose across the entire age range of the study population. Regular PK evaluations throughout the treatment phase, with dose adjustments as necessary, ensure that subjects remain within the target exposure range. Inclusion and exclusion criteria, stopping rules, as well as safety parameters are taking specific account of concomitant conditions in FRDA like cardiomyopathy and decreased insulin tolerance.

No unexpected new toxicities were observed in rats administered MIN-102 in the juvenile toxicology study, supporting administration to patients younger than 18 years. Although based on the mechanism of action and experiences with other molecules of the same class no risk for reproductive function is expected, highly effective methods of contraception and regular pregnancy testing will be implemented for female patients of childbearing potential. Study drug will be immediately discontinued if pregnancy occurs. Safety data are regularly supervised by an independent Data Safety Monitoring Board (DSMB).

On balance, MIN-102 exhibits favorable efficacy and a safe profile for treatment of FRDA, which warrants testing in FRDA patients who currently have no licensed treatment options.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of the study is to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on cervical spinal cord area as assessed by morphometric MRI measurements.

2.2. Primary Endpoint

The primary efficacy endpoint is:

- Change from baseline in spinal cord area cervical segment C2-C3 [mm^2]

2.3. Secondary Objectives

The secondary objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change from baseline in total score of the SARA
- Cervical spinal cord mean, axial and radial diffusivity as assessed by MRI diffusion tensor imaging (DTI)
- Cervical spinal cord tNAA/mIns ratio as assessed by MRS
- MRI quantitative susceptibility mapping (QSM) for iron concentration
- Dentate nuclei volume
- Brain fiber density (FD), fiber cross-section (FC) and fiber density and cross-section (FDC) as assessed by fixel-based analyses (FBA)
- Cerebellar Composite Functional Scale (CCFS), composed of 2 functional tests: 9-hole peg test and clicking [35]
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- Fatigue Severity Scale (FSS)

- Activities of daily living (subscale of the Friedreich's Ataxia Rating Scale [FARS])
- Clinician and patient global impression of improvement
- Safety and tolerability of MIN-102 for up to 48 weeks of treatment and 4 weeks after discontinuation by assessment of AEs, vital signs, 12-lead ECG, echocardiogram, clinical laboratory tests, and palatability.

2.4. Secondary Endpoints

The secondary efficacy endpoints include the change from baseline in:

- Scale for Assessment and Rating of Ataxia
  - Change from baseline in total score of the SARA
- Diffusion tensor imaging fractional anisotropy, mean, radial and axial diffusivity cervical segments C2-C7 [10^{-3} mm^2/s]
- Magnetic resonance spectroscopy tNAA/mIns ratio in spinal cord
- MRI quantitative susceptibility mapping (QSM) for iron concentration [ppb]
- Dentate nuclei volume [mm^3]
- Fixel-based analyses of the brain including FD, FC and FDC
- Cerebellar Composite Functional Scale [35]
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- Fatigue Severity Scale (FSS)
- Activities of Daily Living subscale of FARS
- Clinical Global Impression – Severity (CGI-S)
- Clinical Global Impression – Improvement (CGI-I)
- Patient Global Impression – Improvement (PGI-I)
- Adverse events
- Serious adverse events and suspected unexpected serious adverse drug reactions (SUSARs)
- Vital signs (body weight, blood pressure, pulse rate and body temperature)
- 12-lead ECG (heart rate, PR interval, RR interval, QRS duration, QT interval and corrected QT interval corrected for heart rate using Fridericia's formula [QTcF])
- Echocardiogram with assessment of LVEF
- Physical examination
- Pregnancy test for women of childbearing age
- Palatability assessment [36]

2.5. Exploratory Objectives

The exploratory objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change in the pre-treatment versus post-treatment slope of the SARA

- Neurophysiological parameters as assessed by motor evoked potentials (MEP) as an optional assessment
- Biochemical parameters in plasma: adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells and additional panel of biomarkers related to neurodegeneration and neuroinflammation
- Biochemical parameters in CSF (optional): adiponectin, neurofilament light chain adiponectin, Fatty acid binding protein 4 and additional panel of biomarkers related to neurodegeneration and neuroinflammation
- Volume of further specific brain regions
- DTI parameters, including fractional anisotropy, mean, axial, and radial diffusivity, in specific brain regions

2.6. Exploratory Endpoints

The exploratory efficacy endpoints include:

Clinical

- Change in slope from baseline of the SARA compared from pre-treatment to post-treatment

Neurophysiological

- Motor evoked potentials with central conduction time and amplitude as an optional assessment

Biochemical

- Adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells and additional panel of biomarkers related to neurodegeneration and neuroinflammation in plasma
- Adiponectin, neurofilament light chain adiponectin, Fatty acid binding protein 4 and additional panel of biomarkers related to neurodegeneration and neuroinflammation in CSF (optional)

Imaging

- Change from baseline in the volume of further specific brain regions
- Change from baseline in DTI parameters, including fractional anisotropy, mean, axial, and radial diffusivity, in specific brain regions

2.7. Pharmacokinetic Objectives

- To determine MIN-102 and M3 concentrations in plasma

2.8. Pharmacokinetic Endpoints

- MIN-102 and M3 concentrations in plasma

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

Eligible subjects will be randomized to treatment for 48 weeks with MIN-102 or placebo in a 2:1 ratio after obtaining written informed consent from the subject or, if the subject is a minor, obtaining written informed consent from a parent/legal guardian and written assent from the subject, completion of all screening evaluations within 28 days (4 weeks), and confirmation that the subject has met all inclusion criteria and none of the exclusion criteria.

Motor Evoked Potentials and cerebrospinal fluid sampling are optional and require separate informed consent and assent.

The Screening visit (V-1) occurs after written informed consent is obtained. After the Screening visit, eligible subjects fulfilling all the inclusion and none of the exclusion criteria will be scheduled for a Baseline visit (V0) within a maximum of 28 days after the Screening visit (V-1) and will be randomized to receive an individualized starting dose of MIN-102 or placebo. Subjects will be instructed to take a daily dose of the study treatment at approximately the same time in the morning throughout the entire treatment phase. The administered dose of MIN-102 is intended to achieve a target exposure of 170 $\mu g \cdot hr \cdot mL^{-1}$.

In addition to the Screening visit (V-1) and Baseline visit (V0), subjects will be evaluated at two interim safety visits (ISVs) occurring 2 and 8 weeks after V0 (ISV1 and ISV2), and at 4 (V1), 12 (V2), 24 (V3), 36 (V4), and 48 (V5) weeks after V0.

ISV1 and ISV2 may occur at home, all other visits will be performed on-site. The home visits will be performed by an accredited nurse who is certified in Good Clinical Practice (GCP). Results of all scheduled assessments will be made available to the investigator as soon as possible.

Baseline evaluations will consist of assessments for safety (ECGs, Labs) and tolerability, imaging evaluations (MRI/MRS), evaluations of clinical status on SARA, global clinical rating scales, MEP (optional), and patient questionnaires. Assessment of biochemical markers in plasma and CSF (optional) and blood sampling for plasma levels of MIN-102.

Post-baseline evaluations will consist of assessments for safety (ECGs, Echocardiograms, Labs) and tolerability and blood sampling for plasma levels of MIN-102 at all scheduled on-site visits (except for ISV1 and ISV2), imaging evaluations at V3 and V5, assessment of biochemical markers in plasma at V2, V3, V5, and the follow-up visit (FUV; 4 weeks after last dose of study drug), assessment of biochemical markers in CSF at V3 and V5 (optional), evaluations of clinical status on SARA, global clinical rating scales, MEP (optional), and patient questionnaires at V3 and V5. All assessments for safety, tolerability, and biochemical markers in plasma will also be performed at premature discontinuation.

There will also be regularly scheduled phone calls to the subjects at 6, 10, 16, 20, 28, 32, 40, and 44 weeks after V0. During these calls, the site will ask the subject for changes in concomitant medications and AEs, in particular for symptoms possibly indicative of cardiac failure.

An individualized dose based on PBPK will be chosen to yield a geometric mean AUC_t of approximately 170 µg•hr/mL (± 20%). Blood sampling to determine MIN-102 plasma concentrations will occur before the first dose, and then at each scheduled visit (except ISV1 and ISV2) immediately before each daily dose. The observed plasma concentrations of MIN-102 at V1 will be used to guide dose adjustments. After a potential dose adjustment following PK results from V1, no further dose adjustments are allowed,

except for dose reductions to manage safety or tolerability issues (see sections 3.4.3 and 3.4.4 for further details)

Individual downward adjustments of the dose at any time point after V0 may be implemented by the investigator for safety/tolerability reasons; however, the minimum permitted dose in terms of corresponding volume rounded to the nearest 0.5 mL will be individually calculated for each subject to achieve a plasma exposure of ≥100 µg•hr/mL.

A FUV will occur 4 weeks after last dose of study drug.

3.1.1. Visits and Assessments

Table 1 presents the schedule of assessments for the study. This section describes the study evaluations by visit.

3.1.1.1. Screening Visit (V-1)

The screening phase must be completed within 28 days (4 weeks) prior to the Baseline Visit and should be kept as short as possible. The Screening Visit will consist of the following assessments and procedures:

1. Subject informed consent. The subject or the parent/legal guardian will sign the consent form prior to any study-specific screening procedures. The signed consent form will be retained and archived at the study site, and a copy will be provided to the subject and/or parent/legal guardian. An assent form will be completed with the subject as applicable.
2. Assignment of subject identification number
3. Review of inclusion/exclusion criteria
4. Medical history/concomitant disease review
5. Recording of demographics data
6. Prior medication review
7. Physical examination; findings will be reported as medical history or concomitant disease
8. Assessment of vital signs (height, body weight, blood pressure, and pulse rate)
9. 12-lead ECG recorded in triplicate
10. Echocardiogram
11. Serology (hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody)
12. Laboratory safety tests: hematology (including HbA1c), blood chemistry, prothrombin time, NTpro BNP, urinalysis, urine cytology and serum pregnancy test for female subjects with childbearing potential (within 7 days before the first study drug administration). Note: if the Screening Visit has been performed > 7 days before the Baseline Visit, a home nurse visit may be scheduled to perform the serum test.
13. Evaluation of clinical status with SARA
14. Current medication review

After completion of all screening evaluations, and provided that all inclusion criteria and no exclusion criteria are met, the Baseline Visit will be scheduled.

3.1.1.2. Baseline Visit (V0)

After confirming that all inclusion and no exclusion criteria are met, subjects will be randomized and receive the first dose of study drug on-site. All assessments are performed prior to administration of study drug unless noted below.

The Baseline Visit will consist of the following assessments and procedures:

1. Confirmation of inclusion and exclusion criteria
2. Confirmation of medical history/concomitant disease
3. Update of previous medications
4. Vital signs (body weight, height, blood pressure, pulse rate, and temperature)
5. Pre-dose 12-lead ECG recorded in triplicate
6. Laboratory safety tests: Hematology, blood chemistry, prothrombin time, NTpro BNP, urinalysis, urine cytology and urine and serum pregnancy test for female subjects with childbearing potential.
7. Randomization
8. Dispensation of study drug and patient diary
9. Study drug administration at site
10. Palatability assessment (after study drug administration)
11. 12-lead ECG recorded in triplicate, approximately 3 hours post-dose
12. Evaluation of clinical status with SARA
13. Cerebellar Composite Functional Scale
14. Magnetic resonance imaging/MRS
15. Motor Evoked Potentials assessment (optional)
16. Clinical Global Impression – Severity assessment
17. Fatigue Severity Scale
18. European Quality of Life 5 Dimensions assessment
19. Activity of Daily Living subscale of FARS
20. Blood sampling for biomarkers
21. CSF sampling for biomarkers (optional)
22. Blood sampling for MIN-102 levels
23. Adverse event recording
24. Current medication review

3.1.1.3. Interim Safety Visit 1 (ISV1, at Week 2; possible home visit)

The ISV1 Visit (2 weeks ± 3 days) will consist of the following assessments and procedures:

1. Physical examination for peripheral edema
2. Assessment of vital signs (body weight, blood pressure, and pulse rate)
3. Subject diary review
4. Adverse event recording
5. Current medication review

3.1.1.4. Visit 1 (V1, at Week 4; on site)

The V1 (4 weeks ± 3 days) will consist of the following assessments and procedures:

1. Physical examination for peripheral edema
2. Assessment of vital signs (body weight, blood pressure, and pulse rate)
3. 12-lead ECG recorded in triplicate, approximately 3 hours post-dose
4. Echocardiogram
5. Laboratory safety tests: Hematology, blood chemistry, prothrombin time, NTpro BNP, urinalysis, urine cytology and urine pregnancy test for female subjects with childbearing potential.
6. Subject diary review
7. Blood sampling for MIN-102 levels (pre-dose)
8. Study drug administration at site
9. Palatability assessment (after study drug administration)
10. Adverse event recording
11. Current medication review

3.1.1.5. Phone Call 1 (Week 6)

During Phone Call 1 at Week 6 (± 3 days), the site will discuss AEs and concomitant medications with the subjects.

3.1.1.6. Interim Safety Visit 2 (ISV2, at Week 8; possible Home Visit)

The ISV2 (Week 8 ± 3 days) will consist of the same assessments and procedures performed at ISV1:

1. Physical examination for peripheral edema
2. Assessment of vital signs (body weight, blood pressure, pulse rate)
3. Subject diary review
4. Adverse event recording
5. Current medication review
6. Urine pregnancy test

3.1.1.7. Phone Call 2 (Week 10)

During Phone Call 2 at Week 10 (± 3 days), the investigator will discuss AEs and concomitant medications with the subjects

3.1.1.8. Visit 2 (V2, at Week 12; on site)

The V2 (Week 12 ± 5 days) will consist of the following assessments and procedures:

1. Physical examination
2. Assessment of vital signs (body weight, blood pressure, and pulse rate)
3. Echocardiogram
4. Laboratory safety tests: hematology, blood chemistry, prothrombin time, NTpro BNP, urinalysis, urine cytology and urine pregnancy test for female subjects with childbearing potential.
5. Subject diary review
6. Dispensation of study drug and Patient diary
7. Study drug accountability
8. Blood sampling for biomarkers (pre-dose)
9. Blood sampling for MIN-102 levels (pre-dose)
10. Study drug administration on site.
11. Palatability assessment (after study drug administration)
12. 12-lead ECG recorded in triplicate, approximately 3 hours post-dose
13. Adverse event recording
14. Current medication review

3.1.1.9. Phone Calls 3 and 4 (Weeks 16 and 20)

During Phone Calls 3 and 4 at Weeks 16 and 20 (± 5 days), the investigator will discuss AEs and concomitant medications with the subject and the results of the monthly urine pregnancy test done by the patient at home. Positive results will be confirmed by a serum test as soon as possible.

3.1.1.10. Visit 3 (V3, at Week 24; on site)

The V3 (Week 24 ± 5 days) will consist of the following assessments and procedures:

1. Physical examination
2. Assessment of vital signs (body weight, blood pressure, and pulse rate)
3. Echocardiogram
4. Laboratory safety tests: hematology, blood chemistry, prothrombin time, NTpro BNP, and urinalysis including cytology and urine pregnancy test for female subjects with childbearing potential.
5. Blood sampling for biomarkers (pre-dose)

6. Optional CSF sampling for biomarkers
7. Blood sampling for MIN-102 levels
8. Study drug administration on site
9. Palatability assessment (after study drug administration)
10. 12-lead ECG recorded in triplicate, approximately 3 hours post-dose
11. Subject diary review
12. Dispensation of study drug and Patient diary
13. Study drug accountability
14. Evaluation of clinical status with SARA
15. Cerebellar Composite Functional Scale
16. Magnetic resonance imaging/MRS
17. Motor Evoked Potentials assessment (optional)
18. Clinical Global Impression – Severity and –Improvement assessment
19. Patient Global Impression – Improvement
20. Fatigue Severity Scale
21. European Quality of Life 5 Dimensions assessment
22. Activity of Daily Living subscale of FARS
23. Adverse event recording
24. Current medication review

3.1.1.11. Phone Calls 5 and 6 (Weeks 28 and 32)

During Phone Calls 5 and 6 at Weeks 28 and 32 (± 5 days), the investigator will discuss AEs and concomitant medications with the subjects and the results of the monthly urine pregnancy test done by the patient at home.

3.1.1.12. Visit 4 (V4, at Week 36; on site)

The V4 (Week 36 ± 5 days) will consist of the same assessments and procedures performed at V2:

1. Physical examination
2. Assessment of vital signs (body weight, blood pressure, and pulse rate)
3. Echocardiogram
4. Laboratory safety tests: hematology, blood chemistry, prothrombin time, NTpro BNP, and urinalysis including cytology and urine pregnancy test for female subjects with childbearing potential.
5. Subject diary review
6. Dispensation of study drug and patient diary

7. Study drug accountability
8. Blood sampling for MIN-102 levels (pre-dose)
9. Study drug administration on site
10. Palatability assessment (after study drug administration)
11. 12-lead ECG recorded in triplicate, approximately 3 hours post-dose
12. Adverse event recording
13. Current medication review

3.1.1.13. Phone Call 7 and 8 (Weeks 40 and 44)

During Phone Call 7 and 8 at Weeks 40 and 44 (± 5 days), the investigator will discuss AEs and concomitant medications with the subjects and the results of the monthly urine pregnancy test done by the patient at home.

3.1.1.14. Visit 5/End of Treatment (V5/EOT, at Week 48, on site)

The V5 (Week 48 ± 5 days) will consist of the same assessments and procedures performed at V3 with the exception that study drug will not be dispensed, and temperature will be measured. This is the end of treatment visit.

Any definitive discontinuation of the drug must be considered EOT, either by the end of the study at Visit 5 or by the premature discontinuation of the study drug prior to Visit 5. In both cases, the assessments and procedures scheduled for V5 have to be performed. The EOT visit must be performed as soon as possible after study drug discontinuation. If an MRI has been performed within three months prior to discontinuation, no additional MRI assessment has to be performed. Same applies to SARA, CCFS, MEP (in case the patient has consented), CGI-S, CGI-I, PGI-I, FSS, EQ-5D-5L, and activities of daily living subscale of FARS. If these assessments have been performed within three months prior to discontinuation, no additional assessment will be performed.

The V5/EOT will consist of the following assessments and procedures:

1. Physical examination
2. Assessment of vital signs (body weight, blood pressure, pulse rate, and temperature)
3. 12-lead ECG recorded in triplicate
4. Echocardiogram
5. Laboratory safety tests: hematology (including HbA1c), blood chemistry, prothrombin time, NTpro BNP, and urinalysis including cytology and urine pregnancy test for female subjects with childbearing potential.
6. Subject diary review
7. Blood sampling for biomarkers
8. Optional CSF sampling for biomarkers
9. Blood sampling for MIN-102 levels
10. Study drug accountability

11. Evaluation of clinical status with SARA
12. Cerebellar Composite Functional Scale
13. Magnetic resonance imaging/MRS
14. Motor Evoked Potentials assessment (optional)
15. Clinical Global Impression – Severity and –Improvement assessment
16. Patient Global Impression – Improvement
17. Fatigue Severity Scale
18. European Quality of Life 5 Dimensions assessment
19. Activity of Daily Living subscale of FARS
20. Adverse event recording
21. Current medication review

3.1.1.15. Follow-up Visit

Subjects who either drop out of the study or complete the study will return for a Follow-up Visit 28 (± 5) days after last administration of study drug. The Follow-up Visit will consist of the following assessments and procedures:

1. Physical examination
2. Vital signs (body weight, blood pressure, pulse rate, and temperature)
3. 12-lead ECG recorded in triplicate
4. Echocardiogram
5. Laboratory safety tests: hematology (including HbA1c), blood chemistry, prothrombin time, NTpro BNP, urinalysis including cytology and urine and serum pregnancy test for female subjects with childbearing potential.
6. Adverse event recording
7. Current medication review

3.1.1.16. Unscheduled Visits

Additional (unscheduled) visits during the study may also be performed as necessary in case of any concerns e.g. to follow up on any adverse event. Unscheduled visits will be recorded in the eCRF. In case any unscheduled laboratory tests are necessary during or after the study completion, these should be performed by the centralized companies.

3.1.2. Data and Safety Monitoring Board

An independent DSMB has been established to oversee the safety and efficacy of the study at regular intervals and ad hoc as needed. The composition and function of the DSMB has been described by a Charter signed by all DSMB members.

The DSMB will review all safety information from the study. For this purpose, it will receive safety data at regular intervals during the study. Serious adverse events, SUSARs and AEs leading to withdrawal

will be reported to the DSMB immediately. The DSMB may also request unblinding of data for individual subjects at any time for ad hoc assessment of safety risk.

The DSMB can recommend stopping or modifying the study at any time if unacceptable safety risks become apparent or the number and reason for dropouts is much higher than anticipated. The reasons for dropouts will be carefully investigated. The DSMB can also recommend a downward adjustment of the MIN-102 target exposure range if safety risks are identified.

3.1.3. Study Completion

The sponsor (Minoryx Therapeutics BE SA) reserves the right to discontinue the study, a study site, or multiple study sites for safety or administrative reasons at any time. Should the study be terminated and/or a site closed for whatever reason, all documentation, clinical supplies, and study drug must be returned to the sponsor or its representative.

Upon Last Patient Last Visit (LPLV) of the study, data will be verified and locked and the randomization codes be made available for unblinding of the allocated treatment and data analysis.

The study will be completed when all randomized patients have either performed V5 and FUV, early terminated or discontinued the study, or the study has been stopped based on DSMB recommendation or Sponsor decision. The Clinical Study Report will be written according to the ICH guideline requirements.

3.2. Discussion of Study Design

This is a double-blind, placebo-controlled study and subjects will be randomized in a 2:1 ratio to MIN-102 or placebo.

Section 3.5 discusses the objectives and study endpoints and section 3.4.3 discusses the rationale for MIN-102 dose selection.

3.3. Selection of Study Population

Assuming an approx. 15% drop-out rate, 36 eligible subjects will be enrolled and randomized in a 2:1 ratio to MIN-102 and placebo to achieve 30 evaluable subjects. If the premature discontinuation rate is higher than anticipated, additional subjects may be randomized after mutual agreement with the sponsor to ensure that the study recruits 30 evaluable subjects. The decision to include additional subjects will be documented. Additional statistical information regarding the determination of the sample size is provided in Section 3.6.7.

3.3.1. Inclusion Criteria

Only subjects who meet all of the following criteria will be eligible for inclusion in the study:

1. Signed Informed Consent by the subject or parent/legal guardian, and/or consent or assent for minors as required by national laws.
2. Male and female subjects aged ≥12 and ≤60 years, inclusive, with Friedreich's Ataxia confirmed by genetic testing
3. Total score on SARA of <25.
4. Score on SARA item 1 (gait) ≥2 and ≤6.

5. Male with a potentially fertile partner must be willing to use an acceptable method of contraception for the duration of the study and for 3 months after study drug discontinuation (acceptable methods are: use of a condom with spermicide or use of oral, implantable or injectable contraceptives, or intrauterine devices, or a diaphragm with spermicide or diaphragm with condom) or have had a vasectomy.
6. Female with childbearing potential must be willing to use highly effective contraceptive methods during screening, during the period of drug administration and for 30 days after stopping study drug administration. Highly effective contraception methods include the following:
   - Total abstinence (defined as refraining from heterosexual intercourse during the entire period outlined above),
   - Male or female sterilization,
     - bilateral tubal occlusion
     - vasectomized partner
   - Use of at least one of the following:

     a. Use of oral, injectable, transdermal, intravaginal, or implantable hormonal methods of contraception
     - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral, intravaginal or transdermal.
     - progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable

     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
7. Female patients of childbearing potential must have a negative serum pregnancy test result within 7 days before first administration of study drug

3.3.2. Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Age of onset of disease ≥25 years
2. Left ventricular ejection fraction (LVEF) <55%, on echocardiogram.
3. History of heart failure. Ventricular arrhythmia, supraventricular tachycardia, or having a QTcF time of >480 msec in 3 consecutive ECG recordings taken at least 5 minutes apart.
4. Known intolerance to pioglitazone or other thiazolidinediones.
5. Subjects who are taking or have taken pioglitazone, or other thiazolidinediones, within the past 6 months prior to Screening.
6. Currently participating in or having participated in another interventional clinical study within 2 months prior to Screening.
7. Requiring other prohibited concomitant medication (see Table 4). Note: use of idebenone, coenzyme Q10, antioxidants, riboflavin, thiamine, vitamins C and E is permitted provided the

dose has been constant for ≥3 months before Screening and is kept constant during the entire study.

8. Previous or current history of vesical polyps, bladder cell hyperplasia, or bladder cancer.
9. Previous or current history of other cancer, unless surgically resected and without evidence of recurrence for a minimum of 5 years.
10. Clinically significant anemia (i.e. hemoglobin below 110 g/L).
11. Glycated hemoglobin (HbA1c) levels >6.4% and fasting blood glucose levels ≤ 0.9 times the lower limit of normal and ≥ 1.1 times the upper limit of normal.
12. NT-proB-type natriuretic peptide level (NTpro BNP) >125 pg/mL
13. Abnormal liver enzyme tests for aspartate aminotransferase or alanine aminotransferase of >2 times the upper limit of normal or total bilirubin >1.5 times the upper limit of normal (unless due to Gilbert's syndrome).
14. A positive result on laboratory tests for hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody at screening.
15. Moderate or severe hepatic impairment (groups B and C according to the revised Child-Pugh classification; see Appendix 6.2) [2].
16. Chronic kidney disease (CKD) stages 3a or higher (according to CKD staging by Renal Association with an estimated glomerular filtration rate of <60 ml/min/1.73m^2).
17. Contraindications for MRS/MRI procedure such as subjects with ferromagnetic materials in the body, such as dental braces, spinal rods, aneurysm clips, pacemakers, intraocular metal or cochlear implants.
18. Drug or alcohol abuse in the past 2 years by subject history and/or investigator assessment.
19. Conditions which could modify the absorption of the study drug, such as inflammatory bowel diseases, or stomach or intestinal resection.
20. Inability or unwillingness of the subject or subjects' parents/caregivers to comply with the study procedures.
21. Other medical, neurological, psychiatric, or social conditions that in the investigator's opinion are likely to confound the assessment of safety or efficacy, interfere with study conduct, or unfavorably alter the risk-benefit of subject participation.
22. Pregnant women as confirmed by a positive blood pregnancy test.
23. Female patients intending to breast feed a child while taking study drug or have taken study drug within 30 days after administration of the last dose.

3.3.3. Removal of Patients from the study

A subject must be excluded in the following cases:

- Shows clinical signs of heart failure (dyspnea, orthopnea, pulmonary rales)
- LVEF drops below 50%, or
- LVEF shows an absolute drop of more than 10% from Baseline

More extensive echocardiogram evaluations by a cardiologist with additional measures such as myocardial deformation (strain) assessed by Tissue Doppler Imaging (TDI) or on bidimensional images (speckle tracking) indicate an increased risk of heart failure due to volume overload. These additional evaluations will be performed if LVEF drops by >5% from the Screening value and/or the subject gains >2kg/week or ≥5% weight from the Baseline visit, and/or shows visible edema.

- In case steady elevations of NTpro BNP **>**300 pg/mL occur, the patient will undergo exploration of clinical symptoms indicative of heart failure, a physical examination, and an echocardiogram including the suggested examinations. Treatment with study drug may be suspended during these investigations. If these examinations reveal a clinically significant risk of heart failure by judgment of the investigator and cardiologist, the patient will be excluded from the study. Otherwise, if physical examination shows no signs of heart failure along with preserved LVEF%, study drug, if suspended, may be resumed by judgment of the investigator and administration of diuretics must be considered. After resumption of study drug and administration of diuretics (if no contraindications), unscheduled laboratory assessments of NTpro BNP, clinical examinations and an echocardiogram with evaluations such as myocardial deformation (strain) assessed by Tissue Doppler Imaging (TDI) or on bidimensional images (speckle tracking) should be considered as appropriate. If a risk of heart failure cannot be excluded in the clinical judgment of the investigator and cardiologist, the subject will be permanently discontinued.

Subjects may be discontinued from the study at any time if they do not tolerate the minimum allowed dose or if clinically significant out-of-range laboratory values, clinically significant abnormal findings on physical examination or intolerable AEs put the subject at additional risk, as judged by the investigator.

The parent or legal guardian may withdraw consent and discontinue their child from the study for any reason at any time. The subject may also elect to discontinue himself from the study for any reason at any time.

If a patient is withdrawn from the study, the study monitor will be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the investigator until satisfactory health has returned.

If a female participant becomes pregnant during the study, study drug must be permanently discontinued and the patient will be removed from the study.

The study sponsor has the right to terminate the study at any time.

Suspected Pregnancy

During the study, all females of childbearing potential must be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). All females of childbearing potential will be provided with urine pregnancy tests to perform the test at home between visits at the hospital. Positive results will be confirmed by a serum test as soon as possible.

Male patients must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant.

If a patient or Investigator suspects that the patient may be pregnant, study drug administration must be held until the results of a serum pregnancy test are available. If pregnancy is confirmed, the patient must discontinue taking study drug. The Investigator must immediately report a pregnancy associated with

study drug exposure and record the event. Other appropriate follow-up procedures should be considered if indicated.

Pregnancy is not considered an AE; however, the Investigator must follow a pregnant patient, or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Minoryx Therapeutics BE SA or designee may contact the Investigator to request additional information throughout the course of the pregnancy.

The following post-pregnancy outcomes must be considered SAEs and will require additional reporting in the CRF and on an SAE form.

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

3.4. Treatment

3.4.1. Treatment Assignment

Subjects will be randomized in a 2:1 ratio to MIN-102 or placebo.

3.4.2. Identity of Investigational Product

The active substance in MIN-102 is a small molecule differentiated peroxisome proliferator-activated receptor (PPAR) γ agonist. The active drug substance is a metabolite of pioglitazone, an approved treatment for type 2 diabetes.

Active substance:

MIN-102:	5-[[4-[2-[5-(1-Hydroxyethyl)-2-pyridinyl]ethoxy]phenyl] methyl]-2,4-thiazolidinedione hydrochloride (1:1)
Activity:	PPARγ agonist
In development for:	FRDA
Strength:	15 mg/mL
Dosage form:	Oral suspension
Posology:	Once-daily dosing with a volume specified by the pharmacokinetic specialist to achieve the desired plasma exposure (170 $\mu g \cdot hr \cdot mL^{-1}$)
Manufacturer:	Laboratorium Sanitatis SL

Placebo (matching the active medication visually and by taste)

Activity:	Not applicable
Strength:	Not applicable
Dosage form:	Oral suspension
Posology:	Once-daily dosing with a volume specified by the pharmacokinetic specialist
Manufacturer:	Laboratorium Sanitatis SL

The composition of study medication is shown in the table below:

Table 2: Composition of Study Medication

MIN-102: 15mg/mL suspension	g/100 mL
MIN-102	1.500
Sorbitol	8.000
Colloidal microcrystalline cellulose	1.000
Sodium carboxymethylcellulose	0.500
Sodium saccharin	0.050
Sodium benzoate	0.100
Sodium citrate	0.500
Strawberry flavor	0.015
Citric acid monohydrate	q.s. pH=4.0
Purified water	q.s. 100 mL

Placebo suspension	g/100 mL
Sorbitol	8.000
Colloidal microcrystalline cellulose	1.250
Sodium carboxymethylcellulose	0.750
Sodium saccharin	0.050
Sodium benzoate	0.100
Titanium dioxide	0.050
Microcrystalline cellulose	0.300
Sodium citrate	0.500
Strawberry flavor	0.015
Citric acid monohydrate	q.s. pH=4.4
Purified water	q.s.100 mL

3.4.3. Selection of Dose and Dose Adjustment Criteria

The target dose and exposure in humans are based on the PK findings of the phase 1 study MT-1-01 in healthy adult males and on PBPK modeling, and supported by calculations of MIN-102 exposure with respect to pharmacodynamic effects in preclinical pharmacology. Dose response based on gene expression was determined in *Abcd1* knockout mice. Dose response based on disability scores was established in *Abcd1*/*Abcd2* double-knockout mice serving as an experimental model of autoimmune encephalomyelitis, and in rats serving as an experimental model of autoimmune neuritis. These results consistently confirmed efficacious doses of 50 mg/Kg in mice and 18 mg/Kg in rats which correspond to exposures between 100 to 130 µg•hr/mL. The efficacious concentration range in preclinical models was between 50 and 500 nM, confirming the target exposure of 100 to 130 µg•hr/mL.

Physiologically-based pharmacokinetic modeling for MIN-102 that incorporates CYP3A4 and CYP2C8-mediated metabolism as well as biliary clearance derived from in-vitro data was developed by Certara using the Simcyp software (Simcyp Certara, 2018). During model development, the single-ascending dose (SAD) data were used as the model training dataset and the multiple-ascending dose (MAD) data were used as the model verification dataset. The findings show that CYP induction was low and insignificant. The final MIN-102 model was prospectively applied to estimate an appropriate starting dose for pediatric clinical evaluation. The default Simcyp ontogeny functions for CYP3A4 and CYP2C8 as well as literature ontogeny functions [34] were applied in separate simulations. Allometric scaling was also applied to scale doses based on body size and was compared to the PBPK-derived doses. Since application of the Simcyp default ontogeny versus the Upreti ontogeny functions did not show significant differences in the projected pediatric doses, the Upreti ontogeny functions were selected for the starting doses. An individualized dose based on PBPK will be chosen to yield a geometric mean AUC_t of approximately 170 µg•hr/mL with an expected standard deviation of approximately 20%. Doses for subjects from 12 to 17 years will be determined on a mg/kg basis using body weight at the initiation of treatment (see Table 3). For adults, a fixed dose has been defined by taking the mean bodyweight of the adult population. The main variable in administered dose to actual exposure is the difference in metabolic clearance between individuals; therefore, dose adjustments after the starting dose may be needed.

Table 3 shows the starting dose for various age ranges in children, adolescents, and adults.

Table 3: Starting Dose of MIN-102 by Age

Age Range (years)	**Dose (mg/kg QD)**	**Dose (mL/kg QD)**
≥ 12 to 17	2.2 mg/kg	0,15 mL/kg
Adult (male, 75 Kg)	Fixed dose of 150 mg	Fixed dose of 10 mL
Adult (female, 65 Kg)	Fixed dose of 130 mg	Fixed dose of 8,5 mL

QD = once a day

Blood sampling to determine MIN-102 plasma concentrations will occur at Baseline visit and at each scheduled visit (except ISV1 and ISV2) immediately before each daily dose. The plasma concentration data will be reviewed by an experienced unblinded pharmacokineticist who will analyze blood samples taken at V1 for each patient and will make dose recommendations to achieve the target AUC_t of 170 µg•hr/mL. After the dose recommendation based on the PK results obtained at V1 (week 4), the dose has to be kept constant during the entire study. Only downwards dose adjustments can be performed by the investigator for safety or tolerability issues at any time (see section 3.4.4). Dose adjustment in adolescents (≥ 12 to 17) will be performed following the same algorithm as in adults. The model will be updated and adjusted, if needed, with PK results obtained during the study. Dose recommendations will also be introduced on a random basis for subjects randomized to placebo to preserve the blind.

3.4.4. Dose Reductions due to Safety or Tolerability Issues

Individual downward adjustments of the dose at any time point after V0 may be implemented by the investigator for safety/tolerability reasons. The minimum permitted dose in terms of corresponding volume rounded to the nearest 0.5 mL will be individually calculated for each subject to achieve a plasma exposure of ≥100 µg•hr/mL. Instructions to aid dose reductions based on each subject's individual dose will be made available to the investigator by an unblinded PK expert who is not otherwise involved in

the conduct of the study. Dose reductions will also be made on a random basis for subjects randomized to placebo to preserve the blind.

Dose reductions should follow the guidelines described in the sections below.

3.4.4.1. Dose Reductions Prior to First Pharmacokinetics Results

It is advised not to perform dose reductions until after the initial recommendation from the PK expert. If a dose reduction is deemed necessary by the investigator for safety and/or tolerability reasons prior to the recommendation by the PK expert based on PK results at V1, this reduction should be less than 20% from the starting dose, if possible, to prevent subjects from falling below the minimum efficacious exposure. The percent of dose reduction will be calculated in terms of the corresponding volume rounded to the nearest 0.5 mL.

3.4.4.2. Dose Reductions after Pharmacokinetic Expert Recommendation

If subjects experience safety and/or tolerability issues after a recommendation by the PK expert and the investigator determines a dose reduction is necessary, the dose may be reduced up to 20% of the previous dose recommended by the PK expert. If an additional dose reduction above the initial 20% is required to control safety/tolerability events, the Principal Investigator should discuss the amount of the reduction with the Sponsor. In this case, the maximum allowed dose reduction will be up to 40% of the recommended dose by the PK expert. The percent of dose reduction will be calculated in terms of the corresponding volume rounded to the nearest 0.5 mL

In case the PK expert recommends a dose higher than the dose previously taken by the subject following a dose reduction for safety/tolerability reasons, it is at the discretion of the Principal Investigator to increase the dose or keep it unchanged. However, this dose can't be below the minimum permitted dose.

If AEs resolve after a dose reduction, the dose may be increased again, but cannot be increased above the dose most recently recommended by the PK expert.

Subjects not tolerating the minimum permitted dose will be discontinued from the study.

For those subjects who experience safety/tolerability issues, additional PK analyses may be performed.

3.4.5. Study Drug Administration

Subjects will take 1 dose of MIN-102 at approximately the same time every morning for the duration of the study with or without food. Drug will be administered using a 10-mL syringe. Subjects and parents/caregivers will be instructed to fill the syringe to the appropriate volume, which will be rounded to the nearest 0.5 mL. After each use, the syringe should be washed with clean water and dried externally with paper (until no remains of the study drug suspension are visible on the outer shell of the syringe). Below are the instructions to be given to subjects/parents/caregivers for taking study drug.

At the same time every morning, at the time of study drug administration, take the bottle out of its original packaging, shake it for about 30 seconds, put the bottle on a **horizontal and stable surface** in the provided bottle holder, remove the cap of the bottle, sink the syringe vertically until the tip of the syringe is in the middle of the bottle and extract with the syringe the recommended dose. Empty study drug into the study participant's mouth using the syringe. If you have been advised that the study participant should take more than 5 mL, repeat this step again by placing the syringe into the middle of

the bottle and extracting the required dose and then empty the study drug into the study participant's mouth. After the study participant has taken the daily dose, close the bottle, wash the outside of the syringe with clean water, dry it with a paper towel, and return the bottle and the syringe to its original packaging for storage.

Subjects and/or parents will be provided with a paper diary to record study drug dosing. If a subject misses a dose, he will be instructed to resume the regular, once-daily dosing schedule on the day immediately following the day when the dose was missed. The day when a dose was missed may be recorded in the diary and will be reported to the investigator.

Subjects will be instructed to take study medication at approximately the same time each morning.

It is particularly important that the subject adheres to the schedule of regular study medication intake at the same time each day during the 3 days immediately preceding each visit when where blood samples are be taken for PK. On the day of the visit, subjects must not take study medication until after blood sampling has been completed. The blood sample for PK analysis should be taken approximately within 24h from the previous dose.

3.4.6. Study Drug Interruptions

Administration of study drug may be temporarily interrupted in case a subject experiences safety and/or tolerability issues or other conditions that prevent him from taking study drug. Interruptions should be kept to a minimum.

3.4.7. Packaging, Labeling and Re-Supply

MIN-102 will be provided as an oral suspension in 125-mL bottles. Each bottle will contain 100 mL of suspension with a drug concentration of 15 mg/mL.

Each individual bottle will be packaged in an individual box and labelled. Each kit will contain 15 bottles and 15 syringes packed in individual boxes. Study medication supply will be done through the supply of individual study medication kits. The assignation of study medication kits to a patient will be performed by an Interactive Response Technology (IRT) system.

Study drug supplies will be labelled according to GMP, Annex 13 and applicable regulations.

The Sponsor or the study medication manufacturer will provide study medication to the sites. From there, the medication will be handed to the patient at the applicable visits. Every study medication supply will cover the time period until next visit including a reserve amount. Re-supply of study medication may occur due to the long duration of the study. Medication for re-supply will be packaged in an identical manner to the initial supply.

After completion of the study, the study site is required to return all study drug to the sponsor or its representative.

3.4.8. Storage Conditions

MIN-102 will be stored at the study site in its original packaging at room temperature (25ºC ± 10 ºC). The investigational product must be stored securely. In the event of temperature deviations outside the range of 15ºC to 35ºC, the sponsor will be notified as soon as possible to determine whether the study drug should be quarantined or can be released.

Subjects and parents/caregivers will be instructed to store drug kits in their original packaging at room temperature and in a cool and dry place (i.e., not in the refrigerator).

3.4.9. Concomitant Medications

Any concomitant medications (including over-the-counter medicinal and herbal products) used during the study are to be recorded in the eCRF, specifying the name of the drug, start and stop dates, daily dose, dose regimen, administration route, and reason for administration.

Subjects must be made aware that they must inform the investigator before taking any new treatment during participation in the study, including over-the-counter medicinal and herbal products.

Concomitant physiotherapy and/or subject-initiated regular, scheduled physical activities (such as swimming, walking, or exercising in a gym) will be allowed provided these activities started prior to screening and the same regimen is followed throughout the study period.

Table 4 summarizes prohibited and allowed concomitant medications. Topical applications of prohibited medications are allowed.

Table 4: Prohibited and Allowed Concomitant Medications

Prohibited, and requiring a minimum washout time until screening	Pioglitazone or other thiazolidinediones (6 months wash-out)
Prohibited	Immunosuppressants, corticosteroids, isoniazide, nitrofurantoin
	Moderate to strong CYP3A inhibitors: **Strong:** boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole; **Moderate**: fosamprenavir, imatinib, verapamil, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole
	Moderate to strong CYP2C8 inhibitors: gemfibrozil
Allowed, provided the dose has been stable for ≥3 months prior to screening and is kept constant during the study	N-acetylcysteine, vitamin E, coenzyme Q10, and other non-prescription formulations of vitamins, antioxidants or nutritional supplements
	Idebenone

3.4.10. Treatment Compliance and Drug Accountability

The study drug manufacturer will provide study drug to a site on a per-subject basis. The study site staff will dispense study drug to the subject as detailed in Table 1. Each dispensing will cover the time period until next visit, including a reserve amount.

The investigator is responsible for proper documentation of receipt, storage, and disposition of study drug supplies.

The first dose of study drug will be administered at the study site, with a demonstration of the use of the syringe and bottle by study staff. The subject will take subsequent doses at home. On the days of blood sampling to determine MIN-102 plasma concentration and biomarkers, subjects will be instructed not to take their study drug before the study visit; study drug will be taken after blood sampling as directed by the investigator or study staff. Subjects will be provided with a study diary to record the date, time, and volume of study drug administered each day.

Each subject will be dispensed enough study drug to cover treatment until the next visit, including a reserve amount. Dispensing of the study drug to the subject at the visits will be documented. Subjects and parents/caregivers will be instructed to return empty and partially used bottles to the study site to assess compliance with the dosing schedule.

Compliance will be determined at the study site at each visit after the Baseline visit, when subjects return all previously used and unused bottles. The number of returned bottles will be documented, and the amount of remaining suspension will be assessed by measuring with a ruler (supplied by the sponsor) along the outside of each bottle to determine the amount remaining in millimeters. Compliance will be calculated as the percent of the remaining volume divided by the anticipated volume according to the dose prescribed by the investigator.

Compliance will be summarized overall for the entire study, and by the interval between each scheduled visit. The proportion of subjects who took less than 80% or more than 120% of the prescribed dose will be reported as non-compliant.

Compliance will also be assessed by determination of MIN-102 levels in plasma samples.

3.4.11. Randomization and Blinding

3.4.11.1. Method of Assigning Subjects to Treatment Groups

At the time a subject sign the Informed Consent Form or, if the subject is a minor, the parent/legal guardian signs the Informed Consent Form and the subject signs the assent form, the investigational staff will assign a subject identification number to each subject through the study IRT system.

The subject identification number will be used to identify the subject throughout the study and will be recorded in the electronic case report form. This number must not be re-used. If the full screening visit needs to be repeated, subjects will be screen failed in IRT. A new subject identification number from IRT will be assigned to the subject, to avoid confusion with data from the previous screening. If the full screening visit is not repeated, the subject will keep the same identification number.

Subjects will be randomized using IRT. The assignment to MIN-102 or placebo will be made by a dynamic minimization procedure in a 2:1 ratio using the following factors:

- site
- study

The dynamic minimization will use a stochastic treatment allocation algorithm based on the variance method. No treatment allocation will be deterministic.

Randomization data will be kept strictly confidential and accessible only to authorized persons until the time of unblinding after locking the database upon completion. Only after the study is completed and the data is verified and locked will the randomization codes be made available for data analysis.

3.4.11.2. Blinding

Subjects will be randomly assigned to MIN-102 or placebo in a 2:1 ratio. The following controls will be employed to maintain the double-blind status of the study:

- The oral suspension containing active drug or placebo will be indistinguishable in appearance and taste.
- The packaging and labeling of the bottles containing active drug or placebo will be identical.
- Dose adjustment, if needed to achieve the target exposure, will be decided by an unblinded PK expert from the central laboratory; the PK expert will communicate any dose change required to the investigator.

- In order to preserve the blind, random dose adjustments will be made for subjects receiving placebo.

3.4.11.3. Procedures for Breaking the Blind

The blind should be broken only if knowing the subject's treatment allocation would facilitate specific emergency treatment. If this type of emergency occurs, the investigator will log in in the EDC/IRT system to proceed with breaking the blind. In all cases, the investigator must contact the medical monitor and sponsor as soon as is practical after unblinding has occurred and treatment initiated.

If the blind is broken, the subject will be disqualified from further participation in the study. The date, time, and reason for the unblinding must be documented on the appropriate page of the electronic case report form (eCRF).

3.5. Study Assessments and Variables

3.5.1. Efficacy Assessments

3.5.1.1. Scales

3.5.1.1.1. Scale for Assessment and Rating of Ataxia

The SARA is an 8-item clinical rating scale [37]. Six of the items are scored with points between 0 and 4, gait is scored with points between 0 and 8, and stance is scored with points between 0 and 6. Total maximum score is 40 indicating maximum disability.

3.5.1.1.2. Cerebellar Composite Functional Scale

The CCFS consists of two tests which are carried out with the dominant hand: the 9-hole peg test and clicking [35]. The 9-hole peg test measures the time it takes for the patient to place 9 pegs in holes. In the clicking test, the subject has to press 2 buttons with the index finger of his dominant hand. The buttons are mounted on a board and have to be pressed in an alternating fashion for 10 times. As an outcome, Z-scores are calculated by subtracting the expected time that was obtained from healthy controls from the time measured in the subject.

3.5.1.1.3. Quality of Life Assessment

Quality of life will be assessed using a validated questionnaire that quantifies general health status, the EQ-5D-5L. This is a subject-rated scale with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) where subjects are asked to rate themselves according to presented responses at 5 levels of severity for each dimension. They also rate their overall health on the particular study day on a scale from 0 to 100 points, with 0 indicating the worst possible health. The outcome is the sum of the scores of the responses on the 5 dimensions and the overall rating of health in terms of points.

3.5.1.1.4. Fatigue Severity Scale

Subjects rate their level of fatigue on the FSS [38] by responding to 9 presented statements where a score of 1 means maximum disagreement and 7 means strongest agreement. The outcome is the sum of scores over the 9 items.

3.5.1.1.5. Activities of Daily Living Assessment

Activities of daily living will be assessed by the patients using section II of the FARS [39]. Section II contains 9 items where subjects are rated on a scale between 0 (normal function) and 4 (most severely disturbed function). The scores for the individual 9 items are added to yield the total score.

3.5.1.1.6. Global Impression Scales

The CGI-S is a rating for severity of illness based on a 1-7 point weighted scale that is filled in by the investigator at the start of treatment. It assesses "normal, not at all ill" (1) to "among the most extremely-ill patients" (7). CGI-S will be assessed at all scheduled efficacy visits.

The CGI-I is a tool for assessing total overall improvement as judged by the investigator that considers whether or not the improvement is entirely due to the study medication treatment. It is a 1-7 point weighted scale, going from "very much improved" (1) to "very much worse" (7).

The PGI-I is a tool for assessing improvement as judged by the patient. It is a 1-7 point weighted scale, going from "very much improved" (1) to "very much worse" (7).

3.5.1.2. Magnetic Resonance Imaging and Spectroscopy

A manual will be prepared with detailed instructions for image analysis and evaluation. Analysis will be performed centrally by a separate vendor who is not otherwise involved in the study.

3.5.1.2.1. Volumetric analyses

Brain and cervical spinal cord images will be obtained using a standard T1-weighted sequence. Brain images will be analyzed to determine changes in grey matter and cortical thickness, and changes in the volumes of further specific brain regions. Spinal cord images will be analyzed to determine the cross-sectional area and the eccentricity of the spinal cord.

3.5.1.2.2. Magnetic Resonance Spectroscopy

Magnetic resonance spectra will be measured in the cervical spinal cord to determine the concentration of four metabolites: total creatine, total choline, total NAA (tNAA) and myo-inositol (mIns), as well as the ratio tNAA/mIns.

3.5.1.2.3. Quantitative Susceptibility Mapping (QSM)

QSM will be acquired in the cerebellum, using a gradient echo MRI sequence. It will be used to quantify local tissue properties of the dentate nucleus, which reflect iron concentration. It will also be used to visualize, delineate and estimate the volume of the dentate nucleus.

3.5.1.2.4. Diffusion weighted imaging

Diffusion-weighted images will be acquired in the brain (60 directions) and the spinal cord (30 directions) focusing on the corticospinal tract (CST) and spinal cord fibers. This enables the extraction of diffusion metrics related to the integrity of the CST, further selected brain regions, and spinal cord fibers. High order models using a new fiber-tracking approach known as fixel based analysis (FBA) will be applied to the diffusion data to reconstruct the CST and statistically determine changes to the fibers following treatment as described by Adanyeguh and colleagues this year (Adanyeguh et al, 2018). This method allows the identification of interconnecting fibers in voxel and performs statistical analysis on these specific fibers.

3.5.1.3. Motor Evoked Potentials (optional)

Motor Evoked Potentials are elicited by transcranial magnetic stimulation over the motor cortex (area 4 of Brodmann), allowing for quantification of corticospinal excitability. The MEPs will be assessed for central motor conduction time, which is estimated by subtracting the peripheral conduction time from the motor evoked potential latency elicited by transcranial stimulation.

3.5.2. Pharmacokinetics and Biomarkers

3.5.2.1. Blood Sampling

Blood samples will be taken for analysis of MIN-102 in plasma at V0 before first dose of study medication and pre-dose at the following visits: V1, V2, V3, V4 and V5.

Blood samples will be taken for analysis of Biomarkers at V0 before the first dose of study medication and pre-dose at visit V2, V3 and V5.

Blood samples will be taken via an indwelling intravenous catheter or direct venipuncture. The exact time of blood sampling will be recorded in the eCRF. Details on sample collection, handling, storage and shipping will be described in the laboratory manual.

3.5.2.1.1. Cerebrospinal Fluid Sampling

The CSF assessment for biomarkers will be optional for subjects who give separate informed consent to lumbar puncture and have no contraindications against lumbar puncture, such as risk of bleeding or significant deformities of the spine.

CSF sampling will be performed according to best practice procedures at the site. Qualified medical personnel will perform a lumbar puncture to collect CSF samples of up to 6 mL for analysis of biomarkers. Samples will be collected before the first intake of study medication at V0 and before study medication intake at V3 and V5. The time of CSF sampling and the time of the last intake of study medication before sampling will be recorded. The ICF, protocols for the procedure and protocols for CSF processing are documented separately.

3.5.2.1.2. Drug Concentration and Biomarker Measurements

The analysis of MIN-102 and M3 in plasma will be performed at bioanalytical lab using validated liquid chromatography-mass spectrometry/mass spectrometry methods. The analysis will be conducted in a Good Laboratory Practice (GLP)-compliant facility and laboratory procedures will be in accordance with the current GLP guidelines for the Organization for Economic Cooperation and Development. .

The following biochemical parameters will be analyzed:

- Adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells and additional panel of biomarkers related to neurodegeneration and neuroinflammation in plasma.
- Adiponectin, neurofilament light chain, Fatty acid binding protein 4 and additional panel of biomarkers related to neurodegeneration and neuroinflammation in CSF (optional collection).

The results of the biomarker analyses in plasma and CSF will not be accessible to any staff involved in the conduct of the study until the database is locked.

3.5.3. Assessment of Safety and Tolerability

Safety and tolerability assessments will comprise recording of AEs, clinical laboratory parameter assessment, vital signs, 12-lead ECG, Echocardiograms and physical examination. Assessments will be performed in accordance with Table 1.

3.5.3.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Pre-existing conditions (present before intake of study drug) or pretreatment AEs (onset before intake of study drug) are considered concomitant diseases and should not be recorded as AEs but should be recorded on the concomitant diseases eCRF page. However, if the subject experiences a worsening, increased frequency, or complication of such a concomitant disease, the worsening, increased frequency, or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Test findings and physical examination findings are considered AEs if they:

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study drug dosing (excluding results from blood sampling for MIN-102 levels) or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of an SAE, and/or
- Are considered to be an AE by the investigator or sponsor

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of data collection are not considered AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be reported as an AE.

For more detailed information and for Serious Adverse Events see Section 6.1.

3.5.3.2. Clinical laboratory tests

Blood and urine samples for full clinical laboratory assessments will be collected at study visits as indicated in Table 1. Blood samples will be taken in fasting state (if possible). The following parameters will be analysed: haematology, blood chemistry, prothrombin time, Hb1Ac, NTpro BNP, urinalysis including cytology. A full list of parameters is listed in Appendix section 6.3.

For female subjects with childbearing potential, a blood pregnancy test will be performed at Screening and at subsequent site visits.

In the event the investigator considers a laboratory abnormality in the biochemistry or haematology analysis as "clinically relevant", additional samples for repeated analysis should be collected within a reasonable time, as deemed appropriate and sent to the central laboratory for analysis. A comment

should be provided for these abnormalities on the laboratory report. These laboratory samples should be identified as "unscheduled" samples.

The clinical laboratory will flag laboratory test values that are outside of the normal range and the investigator will give his/her overall interpretation of the results. Clinically significant findings will be recorded as AEs and a relationship to study medication will be indicated and recorded in the CRF.

Transaminase increases combined with total bilirubin (TBIL) increases following MIN-102 exposure may be indicative of DILI and should be considered clinically important events. Laboratory parameters indicating potential DILI are specified in Section 6.4 and will be monitored according to the FDA Guidance "Guidance for Industry – Drug Induced Liver Injury".

3.5.3.3. Physical Examination

Physical examinations will be performed at the designated on-site visits. Physical examination includes evaluation of the heart, lungs, abdomen, extremities, and skin, with specific attention to the presence of peripheral edema and signs or symptoms of heart failure. At the optional home visits (ISV1 and ISV2) and at visit 1, the physical exam will only include evaluation for the presence of peripheral edema. The physical examination will be conducted by the investigator or a medically qualified delegate.

3.5.3.4. Vital Signs

Systolic and diastolic blood pressure and pulse rate will be recorded after the subject has been resting in the supine position for at least 5 minutes. Assessments will be made using an automated device using the same arm throughout the study, if possible. All assessments at V0 and later are performed immediately prior to study medication administration. Temperature measurements will only be performed at V0, V5 and FUV, and height only at the Screening Visit.

3.5.3.5. Electrocardiogram

A standard 12 lead ECG will be recorded after the patient has been resting in the supine position for at least 5 minutes. The following ECG parameters will be recorded using an ECG machine equipped with computer-based interval measurement: heart rate, PR interval, RR interval, QRS duration, and QTcF. The investigator will provide interpretation of the ECG profile. The ECG has to be recorded in triplicate with 3 serial readings performed 5 minutes apart approximately 3 hours after the daily dose has been administered (unless specified otherwise; see Table 1).

3.5.3.6. Echocardiogram

An echocardiogram will be performed at the Screening visit to exclude patients with left ventricular abnormalities. An echocardiogram will be repeated at all on site visits (as described in Table 1). If LVEF drops by >5% from the Screening value and/or the subject gains ≥5% weight from the Baseline visit, and/or shows visible edema, more extensive echocardiogram evaluations will be completed by a cardiologist to determine whether there is a risk of heart failure due to volume overload. These additional evaluations may include additional measures such as myocardial deformation (strain) assessed by Tissue Doppler Imaging (TDI) or on bidimensional images (speckle tracking). A subject must be excluded in any case if LVEF drops below 50% or LVEF shows an absolute drop of more than 10% from Baseline. For echocardiogram evaluations in conjunction with increases of NTpro BNP, refer to section 3.3.3.

Echocardiograms will be evaluated locally to determine whether additional evaluations are required, or whether the LVEF values demand the exclusion of subjects from the study. All echocardiograms are sent to a centralized vendor for full evaluation.

3.5.3.7. Palatability Assessment

The palatability of the study drug will be determined by a palatability assessment [36] directly after administration of the daily dose at the Baseline (V0), V1, and V1 through V5. For the assessment of palatability, patients are presented a 5-point hedonic scale where they rate the taste from "super-good" to "super-bad".

3.6. Statistics

3.6.1. Analysis Sets

The analysis sets are defined in Table 5. The primary analyses will be conducted using the mITT analysis set. In addition, a per-protocol (PP) analysis will be conducted.

Table 5: Analysis Sets

Analysis Set	Subjects Included
Safety analysis set	All subjects who took at least 1 dose (partial or complete) of study drug
mITT analysis set	All subjects who took at least 1 dose (partial or complete) of study drug and had at least 1 post-baseline spinal cord area cervical segment C2-C3 measurement and SARA assessment at the same visit
PP analysis set	All subjects in the mITT analysis set without a major protocol deviation

mITT = modified intent-to-treat; PP = per-protocol

3.6.2. Protocol Deviations

All protocol deviations will be summarized in the clinical study report. After database closure, the study team will assess all protocol deviations on a subject-by-subject basis to ascertain how the deviation affects subject inclusion into the various analysis sets. Any deviation may affect the subject's eligibility for 1 or more of the analysis sets. The impact of protocol deviations on assessment of the primary endpoint and the handling of missing/invalid data will be carefully investigated.

3.6.3. Statistical and Analytical Plans

Full details of the statistical methods to be used for analysis of study data will be provided in the Statistical Analysis Plan.

3.6.4. Efficacy Evaluation

3.6.4.1. Primary Endpoint

The primary endpoint for this study is:

- Change from baseline in spinal cord area cervical segment C2-C3 [mm2]

The endpoint will be compared between the two treatment groups based on an analysis of covariance (ANCOVA) model for change from baseline at 48 weeks with terms for treatment group and baseline value. In this study, formal statistical significance on the individual endpoints is not sought. The study

will look equally for clinically meaningful effects based on the effect sizes and associated 95% confidence intervals with p-values used as a guide to activity.

3.6.4.2. Secondary Endpoints

The secondary endpoints, with the exception of CGI-I and PGI-I, will be analyzed based on the two-sample t-test or analysis of covariance, depending on whether a corresponding baseline/pre-treatment measurement of that variable is available. Both CGI-I and PGI-I will be evaluated based on the two-sample t-test. Formal statistical significance is not anticipated and the focus for interpretation will be the effect sizes and associated 95% confidence intervals.

3.6.4.3. Exploratory Endpoints

Exploratory analyses for this study include:

- A rank analysis based on the O'Brien procedure [40] that constructs a two-component composite variable using the sum of the ranks of each of change in spinal cord area and SARA total score
- An analysis of covariance of the SARA scale taking into account decline prior to entry into the study. Decline on SARA prior to randomization will be calculated using the two most recent assessments prior to Screening with an interval of ≥10 months and ≤14 months between them, and the last assessment at least 24 weeks prior to Screening. The SARA assessment at Screening will serve as the third datapoint to calculate decline prior to treatment. Decline on SARA on treatment will be calculated using the SARA assessments at Visits V0, V3, and V5. The changes in decline before randomization versus the decline on treatment will be compared between the two treatment groups. This is an optional analysis in all patients who have two SARA assessments prior to Screening and requires separate informed consent by the patients to using these data.
- A graphical analysis that investigates scatter plots (x-axis = SARA, y-axis = spinal cord area) for the co-primary endpoints between the treatment groups

3.6.5. Safety and Tolerability Evaluation

Safety assessments will focus on the type, severity, and frequency of individual AEs and laboratory tests, vital signs, and ECG abnormalities. The analyses will generally be descriptive in nature and will be based on the safety population.

Adverse event data will be displayed in listings by subject. The number and percentage of subjects with AEs will be tabulated by system organ class (SOC) and preferred term (PT). A subject with multiple AEs within a SOC or PT will be counted once toward the total for the total for the SOC or PT. Further AE tables, for example, by severity, relationship, or outcome will be presented if the number of events makes such information useful.

Other safety parameters will be displayed by visit and other key variables as applicable. Summary statistics for continuous variables will include: n (number of subjects with non-missing values), mean, SD, median, minimum, and maximum. Statistics for categorical variables will consist of counts and percentages of subjects falling into each category (frequency tables). If appropriate, change from baseline will be described using summary statistics for continuous variables and by shift tables (including absolute and relative frequencies) for categorical variables.

The Medical Dictionary for Regulatory Activities (latest version) will be used for coding AEs and medical history (past and/or concomitant disease). The World Health Organization Drug Dictionary (latest version) will be used to code concomitant and previous medications.

3.6.6. Interim Analysis

There will be no interim analysis.

3.6.7. Determination of Sample Size

This is a phase 2a study without available data to support a formal power calculation, and therefore formal statistical significance is not sought.

4. STUDY MANAGEMENT

4.1. Approval and Consent

4.1.1.1. Regulatory Guidelines

The study will be performed under GCP in accordance with the guidelines of the ICH, Declaration of Helsinki, and in accordance with U.S. Investigational New Drug regulations (21 Code of Federal Regulations [CFR] 312) and local laws (as applicable).

4.1.1.2. Institutional Review Board (IRB)/Independent Ethic Committee (IEC)

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, Investigator's Brochure, protocol amendments, consent forms, subject information sheets, and advertising materials for recruitment of subjects. No drug will be shipped to a site until written IRB/IEC authorization has been received by the sponsor or its representative.

In the U.S., the investigator is also responsible for notifying the IRB of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Minoryx Therapeutics BE SA will provide this information to the investigator. Outside the US, Sponsor or CRO will perform notification or submissions to IRBs.

Progress reports, notifications of serious adverse drug reactions, and predefined protocol deviations will be provided to the IRB/IEC according to local regulations and guidelines.

4.1.1.3. Written Informed Consent

For each study subject, written informed consent must be obtained from the parent/legal guardian prior to initiating any protocol-related procedures. As applicable, assent of the subject will be obtained. As part of this procedure, the investigator or an associate must explain orally and in writing the nature, duration, and purpose of the study and the action of the drug in such a manner that the subject/parent is aware of the potential risks, inconveniences, or adverse effects. The parent/legal guardian should be informed that the subject may withdraw from the study at any time. The consent process should provide the parent/legal guardian with all information required by local regulations and ICH guidelines. The investigator will provide the sponsor or its representative with a copy of the IRB-approved consent form prior to the start of the study.

4.2. Financing and Insurance

Prior to study commencement, the sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the sponsor (or its designee).

The Sponsor has insurance coverage for trial-related, medicine-induced injury, and other liabilities incurred during clinical trials which will provide compensation for any study-related injury. The Sponsor will provide local country-specific insurance, as required.

4.3. Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at a site or multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated, and/or the site closed for whatever reason, all documentation, clinical supplies, and study drug pertaining to the study must be returned to the sponsor or its representative.

4.4. Changes to Final Study Protocol

All protocol amendments must be submitted to the IEC/IRB. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation. However, Minoryx Therapeutics BE SA, at any time, can amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification. In the event of a protocol modification, the subject consent form may require similar modifications with subsequent IRB/IEC approval and re-consenting of subjects.

4.5. Notification of Study Completion or Discontinuation

The Health Authority and the IRB/IEC in each country will be notified as per applicable regulations.

4.6. Quality Assurance and Quality Control

4.6.1.1. Study Monitoring

This study will be regularly monitored at all stages of development by the clinical research personnel employed by the sponsor or its representative contract research organization to ensure adherence to the study protocol, to the International Conference on Harmonisation (ICH) GCP and any applicable regulatory requirements.

The progress of the study will be monitored by on-site visits and written, e-mail, and telephone communications between personnel at the study site and the sponsor. The investigator will allow sponsor monitors or designee(s) to inspect all eCRFs; subject records (source documents); signed consent forms; records of study drug receipt, storage, and disposition; and regulatory files related to the study.

The study monitor is responsible for visiting sites at regular intervals throughout the study according to the clinical monitoring plan to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The

monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate any deviations from the protocol, standard operating procedures, GCP, and applicable regulations to the investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

By signing this protocol, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

Accurate and reliable data collection will be assured by the study monitor's 100% verification and cross-check of the eCRFs against source documents and the investigator's records. Note that a variety of original documents, data, and records may be considered as source documents in this study. Any data to be recorded directly in the eCRF (to be considered as source data) will be identified at the start of the study.

The investigator and appropriate personnel will be requested to attend meetings and/or trainings required by the sponsor or its representative contract research organization to assure acceptable protocol execution.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol.

4.6.1.2. Audits and Inspections

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from the sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The study may also be subject to audit or inspection by regulatory authorities or the IRB/IEC.

If such an audit occurs, the investigator must allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, appropriate regulatory authorities, and the IRB/IEC for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, as clinically appropriate. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

4.6.1.3. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of sponsor or its designee will provide instructions for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, imaging and clinical assessments, a record of clinical safety laboratory sample collection, drug administration, AEs, and final evaluation.

The eCRFs must be completed for each subject who signs a consent form and undergoes any screening procedure. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. All study-related data for these subjects will be maintained in the medical records at the site. All study-related data for subjects will be maintained in the medical records at the site.

The eCRF data entry will be completed on the day of the visit or as soon as possible thereafter. The investigator must electronically sign and date the eCRF. The signature will indicate that the investigator has reviewed the data and data queries recorded on eCRFs and the site notifications and that he/she agrees with the content. After the completion of the study, eCRFs, including the audit trail, will be returned to the sponsor and stored in the archives.

4.6.1.4. Data Management

Each subject will be identified in the database by a unique subject identification number.

To ensure the quality of clinical data across all subjects and sites, a clinical data management review on subject data will be performed according to specifications given to the sponsor or designee. Data will be vetted electronically and/or manually as appropriate. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP.

For eCRFs, the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and/or manually raised by reviewers will be generated within the electronic data capture application and also resolved within the eCRF application by the investigator.

Data received from external sources such as central laboratories will be reconciled with the clinical database.

Serious AEs in the clinical database will be reconciled with the safety database.

All medical history (except terms pre-specified on the eCRF) and AEs will be coded using the Medical Dictionary for Regulatory Activities. All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

At the time of database lock, the clinical database will undergo a quality control audit check to ensure accuracy of the data. The audit will involve a comparison of eCRF values with values from data listings generated from the clinical database. Values identified as critical safety and efficacy variables will be confirmed for 100% of the subjects. In addition, a random sample of subjects will be selected to have all data values checked. The number of subjects whose data will be randomly reviewed will be determined to provide sufficient checks of accuracy of the clinical database.

4.6.1.5. Storage and Retention of Study Records

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Investigator Site File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities.

Essential documents include the following:

- Subject files containing completed consent forms and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to starting a clinical study, and all correspondence to and from the IRB/IEC and the sponsor.
- Records related to the investigational product, including acknowledgment of receipt at site, accountability records, final reconciliation, and applicable correspondence

In addition, all original source documents must be maintained by sites and be readily available. Source documents include all recordings and observations or notations of clinical activities and all reports and records supporting entries in the eCRFs and necessary for the evaluation and reconstruction of the clinical study.

Essential documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records, inventory of study product), records of subjects, source documents, monitoring visit logs, data correction forms, and other sponsor correspondence pertaining to the study must be kept in appropriate study files in a secure location at the site.

The investigator must arrange for retention of study records at the site. The duration of the retention period must meet the requirements of the relevant regulatory authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location

Prior to transfer or destruction of study records, the sponsor must be notified in writing and be given the opportunity to further store such records.

The investigator agrees to comply with all applicable laws and regulations related to the privacy and protection of patient health information.

4.6.1.6. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality.

Records will be kept in a secure storage area with limited access.

Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the authorities, or the EC.

Other patient confidentiality will be addressed in the clinical trial agreement with the sites and in the informed consent form signed by each study participant.

The investigator must ensure that the study is performed in accordance with the applicable data protection laws, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation or GDPR). The investigator must ensure that the subject's anonymity is maintained, and keep in strict confidence documents not de-identified (e.g., signed informed consent form). The investigator must also provide all reasonable assistance to the sponsor in the exercise of their duties as Data Controller (as defined by the GDPR) for the study.

4.7. Use of Study Findings

By signing the study protocol, the investigator agrees to the use of study results for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's

name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative.

4.8. Publication Policy

The intention of this study will be to publish the results at study conclusion. All information obtained during the conduct of the study will be regarded as confidential, and written permission from the sponsor is required prior to disclosing any information related to the study. A formal publication of data collected as a result of the study will be considered a joint publication by all investigators and appropriate sponsor personnel. Authorship will be determined by mutual agreement. Submission to the sponsor for review and comment is required prior to submission to the publisher. This requirement should not be construed as a means of restricting publication, but is intended solely to ensure concurrence regarding data, evaluations, and conclusions, and to provide an opportunity to share with the investigator any new or unpublished information of which he or she may be unaware

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6. APPENDICES

6.1. Adverse Events

6.1.1. Definitions

6.1.1.1. Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE. This refers to an event that, in the view of either the investigator or sponsor, places the subject at immediate risk of death. It does not include an AE that, if it had occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization. This refers to hospital admission required for treatment of the AE. This does not include "social or convenience" hospitalization for nonmedical causes such as lack of transportation to home; admissions of less than 24 hours for purposes of observation; confinement in, for example, a respite unit, a skilled nursing unit, or rehabilitation facility; or confinement due to a planned or an unplanned reason unrelated to the study. Emergency room visits that do not result in admission to the hospital should be evaluated for 1 of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Note that all SAEs are also AEs.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time the first dose of study drug is administered until the safety follow-up visit indicated in Table 1). Certain pregnancy outcomes will require submission as a SAE.

6.1.1.2. Unexpected Adverse Event or Serious Adverse Event

An AE or SAE is considered "unexpected" if it is not listed in the Investigators Brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular

accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

6.1.1.3. Suspected Unexpected Serious Adverse Reaction

A SUSAR is an SAE that is unexpected and has a reasonable possibility of being caused by the drug (i.e., is an adverse reaction).

6.1.1.4. Severity of Adverse Events

The severity of AEs will be graded using the most current version of the Common Terminology Criteria for Adverse Events 5-point scale:

- Mild (grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (grade 2): minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
- Severe (grade 3): severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life threatening (grade 4): life-threatening consequences; urgent intervention indicated
- Death (grade 5): death related to AE

It is emphasized that the term "severe" is a measure of severity; thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe but may not be clinically serious.

6.1.1.5. Relationship of Adverse Events to Study Drug

The relationship of any AE to the study drug will be assessed and graded as related or not related. Adverse events will be considered "related" when there is a reasonable possibility that the drug caused the event. Adverse events will be considered "unrelated" when it appears very unlikely that the drug caused the event, such as when an alternate cause of the event is evident.

6.1.2. Recording and Reporting Adverse Events

6.1.2.1. Recording and Reporting of All Adverse Events

Adverse events will be recorded from the Baseline Visit (after first dose of study drug) until completion of the Follow-up Visit. Any clinically significant observation, as assessed by the investigator, in clinical laboratory parameters, 12-lead ECG, vital signs, or physical examinations may be recorded as an AE.

Adverse events will be elicited by asking the subject non-leading questions (e.g., "How do/did you feel?") at various times before and after study drug administration and at regular intervals throughout the study. Adverse events may also be spontaneously reported by the subject.

Subjects and parents/caregivers should be instructed to record AEs in the subject diary on a daily basis between visits. They should be told to report any untoward medical occurrence during the clinical study

from the time of first dose of study drug to the end study participation (at least 4 weeks after last dose of study drug).

During the defined AE collection period, the investigator will record all elicited and spontaneously reported AEs on the eCRF. The investigator will also transcribe any AEs recorded in the subject's paper diary on the eCRF. Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms should not be recorded as additional AEs. If a diagnosis is unknown, signs and symptoms should be recorded as AEs.

The severity of AEs will be rated as mild, moderate, severe, life threatening, or death, and the relationship between the AE and the study drug will be indicated as not related or related. Other information to be collected for AEs include onset date, end date, frequency, seriousness, action taken, and outcome.

6.1.2.2. Recording and Reporting of Serious Adverse Events

All SAEs must be reported by the investigator to the sponsor or designee by Fax or e-mail (See page 4 of this protocol for contact details). Any SAE that occurs between the signature of the ICF and 28 days after the last dose of study drug must be promptly (not later than 1 business day after the study site becomes aware of its occurrence) reported to the sponsor or designee. Any SAEs occurring more than 28 days after the last dose of study drug should be reported to the sponsor only if the investigator suspects a causal relationship to the study drug.

The initial SAE report should be submitted on the SAE Form and requires the following information (at a minimum):

- Subject identification number
- Reporter name/site number
- Adverse event term
- Suspect investigational product
- Relationship of the AE to study drug
- Criteria for seriousness

If there are any questions regarding the reporting of SAEs, the investigator should contact sponsor or designee. For protocol- or safety-related issues, the investigator should contact the Medical Monitor.

6.1.3. Regulatory Agencies, Institutional Review Board /Independent Ethic Committees, and Data Safety Monitoring Board Reporting

The sponsor or designee will submit all safety updates and periodic reports to the European Medicines Agency (EMA) and investigators in accordance with EMA regulations or other applicable regulations.

For each SAE, the investigator and sponsor (or designee) will independently assess whether there is a reasonable possibility that the event may have been caused by the study drug (is "drug-related"). If the SAE is assessed to be both drug-related and unexpected, the sponsor or designee will report it to the appropriate regulatory authorities and notify investigators as required by applicable local regulations.

The sponsor or designee will submit an expedited report of SUSARs to the EMA no later than 15 calendar days after the sponsor or designee first had knowledge of the adverse reaction. In fatal or life-threatening cases, a report will be submitted within 7 calendar days.

It is the responsibility of the investigator to promptly notify the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of any Investigational New Drug Application safety reports or other matters involving risk to subjects as mandated by the IRB/IEC.

The sponsor will provide the DSMB with data on all SAEs on an ongoing basis.

6.1.4. Follow-up of Adverse Events

Any AE will be followed until the event returns to baseline or becomes stable with no further change expected. In the event of an abnormality considered to be clinically significant by the investigating physician, subjects will be followed with appropriate medical management until values are considered to be clinically acceptable and no further change is expected; referral or collaborative care will be arranged if required.

All SAEs should be monitored until they have resolved or stabilized.

6.2. Child-Pugh Score for Hepatic Impairment

This classification was initially developed to assess the operative risk in cirrhotic patients who recovered from variceal bleeding. The revised score consists of 5 domains selected by clinical experience: ascites, encephalopathy, prothrombin time, and serum levels of bilirubin and albumin. Each measure is scored 1–3, with 3 indicating most severe abnormality.

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation(s) **OR** International Normalized Ratio	<4.0 <1.7	4.0–6.0 1.7-2.3	>6.0 >2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

The sum of scores classifies patients in class A, B, or C:

Points	**Class**
5–6	A
7–9	B
10–15	C

6.3. Clinical Laboratory Parameters

The following laboratory parameters will be assessed:

- Blood chemistry: total bilirubin, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, creatinine, urea, uric acid, cholesterol, triglycerides, total protein, albumin, NTpro BNP, glucose, inorganic phosphate, sodium, potassium, calcium, chloride, and bicarbonate (at all visits)
- Prothrombin time
- Hematology: HbA1c (only at V-1, V5, and follow up), leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, lymphocytes, monocytes, eosinophils, basophils, neutrophils, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Urinalysis (qualitative): hemoglobin, urobilinogen, ketones, glucose, protein, bilirubin, leukocytes, pH, and nitrite
- Cytological examination for presence of abnormalities in bladder epithelial cells
- Serology: hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody (only at V-1).

6.4. Drug-Induced Liver Injury

6.4.1. Introduction

Transaminase increases combined with total bilirubin (TBIL) increases following MIN-102 exposure may be indicative of DILI and should be considered clinically important events. Laboratory parameters indicating potential DILI will be monitored according to the FDA Guidance "Guidance for Industry – Drug Induced Liver Injury".

6.4.2. DILI Monitoring Schedule

Monitoring for DILI will include tests for total bilirubin (TBIL, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), and prothrombin time at the following post-Baseline visits: Visit 1 (V1), Visit 2 (V2), Visit 3 (V3), Visit 4 (V4), Visit 5 (V5) and follow up visit (FUV).

6.4.3. DILI Follow-up

Detection:

For elevations in transaminases or bilirubin (AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN) in the absence of cholestasis (serum alkaline phosphatase < 2 x upper limit of normal (ULN) and no clinical evidence of biliary obstruction), the investigator will immediately request that the patient attend an unscheduled visit within 48 hours. In case close observation cannot be performed, study drug will be interrupted. If symptoms persist or repeat testing does not show a clinically significant reduction in levels of transaminase, INR, and/or bilirubin, a close observation will be initiated to determine whether the abnormalities are improving or worsening and study drug will be interrupted.

Close observation will include:

- Repeating liver enzyme and serum bilirubin tests two times per week. Frequency of retesting can decrease to once a week if abnormalities stabilize and the subject is asymptomatic.

Additional laboratories (such as fractionated bilirubin, other chemistries, and complete blood count [CBC]) may be ordered as necessary to more fully assess the subject's clinical status and/or the cause or effects of the hepatic abnormalities.

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets in addition to exposure to environmental chemical agents.
- Further testing for acute hepatitis A, B, C, or E infection, other hepatotropic viral infection (cytomegalovirus, Epstein-Barr, or herpes simplex) or autoimmune hepatitis may be ordered if needed to clarify or confirm the cause of the liver function test abnormalities. Additional testing such as liver imaging or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

Additionally, study drug must be immediately discontinued in the following situations and patients must be followed until full resolution:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)

Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state.

6.4.4. Communication Flow

In this protocol, a central lab is used. Investigators should review all results issued by the central laboratory in an ongoing basis.

In case liver function test results are abnormal, the investigator will inform the patient that an unscheduled visit should be scheduled, at site if possible, as soon as possible, preferably within 48 hours. If the patient lives far away from the trial site, the investigator will inform the home nurse to obtain another blood sample. The following measurements will be performed at this unscheduled visit: TBIL, alkaline phosphatase, AST, ALT, and INR, as well as other tests (e.g., additional chemistries and CBC) deemed necessary by the investigator to more fully assess the subject's clinical status and/or the cause or effects of the hepatic abnormalities. Results will be made available to the investigator to be evaluated as soon as possible.

The investigator should communicate any events that meet the DILI as a serious adverse event (SAE) in 24 hours, as per procedures described in the protocol in Section 6.1. All complementary tests performed should be explained. Any confirmed DILI events will be reported to Competent Authorities as suspected unexpected serious adverse reactions (SUSARs) as described in the protocol in Section 6.1.1.3.

All laboratory results analyzed by the central laboratory will be available in the database. All information regarding a potential DILI event will be recorded in the SAE forms and will be included in Suspect Adverse Reaction Report CIOMs form.

6.5. Protocol Amendment Changes

Section Changed	Previous Protocol Version	Explanation of Change	Reason of change	Impact on subjects
Cover Page	3.0 dated 31 October 2019	Creation of a new version (4.0 dated 25 February 2020)	Versioning update	None
Synopsis Exploratory Objectives and Pharmacokinetic endpoints	3.0 dated 31 October 2019	Exploratory objectives have been added	The recorded MRI data will allow the analysis of more exploratory parameters than initially planned in the previous protocol version.	None, since the evaluation of additional parameters does not demand a change in the MRI acquisition parameters or additional time spent in the scanner by study subjects
Flow chart	3.0 dated 31 October 2019	Added analysis of M3 in plasma in addition to MIN-102	Pharmacokinetic parameters of the main metabolite, M3, will also be analyzed	None
Section 2.5 Exploratory objectives	3.0 dated 31 October 2019	Exploratory objectives have been added	As above.	None
Section 2.6 Exploratory endpoints	3.0 dated 31 October 2019	Exploratory endpoints have been added	As above.	None
Section 2.7 Pharmacokinetic objectives	3.0 dated 31 October 2019	Added analysis of M3 in plasma in addition to MIN-102	Pharmacokinetic parameters of the main metabolite, M3, will also be analyzed	None

Section 2.8 Pharmacokinetic endpoints	3.0 dated 31 October 2019	Added analysis of M3 in plasma in addition to MIN-102	Pharmacokinetic parameters of the main metabolite, M3, will also be analyzed	None
Section 3.5.1.2.1	3.0 dated 31 October 2019	Volume changes in further brain regions have been added as parameters.	To address the analysis of the additional exploratory endpoints	None
Section 3.5.2.1.2	3.0 dated 31 October 2019	Added analysis of M3 in plasma	Pharmacokinetic parameters of the main metabolite, M3, will also be analyzed	None
Section 3.6.4.1	3.0 dated 31 October 2019	The statistical approach to the analysis of the primary endpoint had been changed from a two-sample t-test to an analysis of covariance (ANCOVA) model for change from baseline at 48 weeks with terms for treatment group and baseline value.	The new statistical approach is considered more adequate.	None
Throughout the protocol	3.0 dated 31 October 2019	Miscellaneous typographic errors corrected	To correct typographical and formatting errors	None

eSAP2 Statistical Analysis Plan

Sponsor:	Minoryx Therapeutics BE SA
Protocol Title:	A double-blind, placebo-controlled study on the effect of MIN-102 on biochemical, imaging neurophysiological, and clinical markers in patients with Friedreich's Ataxia.
Study Code:	MT-2-03

For IDDI:

Authors: Nicolas Dubois – Biostatistician

Celine Mauquoi – Senior Biostatistician

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For Sponsor:

Reviewer: Uwe Meya- Chief Medical Officer

Table of Contents

1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
ANCOVA	Analysis of covariance
AUC	Area under the concentration-time curve
CCFS	Cerebellar Composite Functional Scale
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity
COVID-19	Corona Virus Disease 2019
Cmin	Minimum plasma concentration
CRF	Case Report Form
CSF	Cerebrospinal fluid
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5 Dimensions
FARS	Friedreich's Ataxia Rating Scale
FBA	Fixel-based analyses fiber
FDC	Fiber density and cross-section
FRDA	Friedreich's ataxia
FSS	Fatigue Severity Scale
FUV	Follow-Up Visit
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
kg	Kilogram
ISV	Interim Safety Visit
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MEP	Motor Evoked Potentials
mIns	Myo-inositol
mITT	Modified Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities

mL	Milliliter
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NCI	National Cancer Institute
NRF1	Nuclear Respiratory Factor 1
NT-pro BNP	NT-proB-type natriuretic peptide level
PBPK	Physiologically Based Pharmacokinetic modeling
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator
PGI-I	Patient Global Impressions – Improvement
PK	Pharmacokinetics
PP	Per Protocol
QSM	Quantitative Susceptibility Mapping
QTcF	Corrected QT interval by Fredericia
SAE	Serious Adverse Event
SARA	Scale for the Assessment and Rating of Ataxia
SAS	Statistical Analysis System
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TFAM	Mitochondrial Transcription Factor A
tNAA	total N-acetylaspartate
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
y.o.	Years old

2. Introduction

This Statistical Analysis Plan was written for the clinical trial MT-2-03 conducted in 5 sites in Europe. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on cervical spinal cord area as assessed by morphometric MRI measurements.

3.1.2 Secondary Objectives

The secondary objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change from baseline in the total score of the SARA
- Cervical spinal cord mean, axial and radial diffusivity as assessed by MRI diffusion tensor imaging (DTI)
- Cervical spinal cord tNAA/mIns ratio as assessed by MRS
- MRI quantitative susceptibility mapping (QSM) for iron concentration
- Dentate nuclei volume
- Brain fiber density, fiber cross-section and fiber density and cross-section (FDC) as assessed by fixel-based analyses (FBA)
- Cerebellar Composite Functional Scale (CCFS), composed of 2 functional tests: 9-hole peg test and clicking
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- Fatigue Severity Scale (FSS)
- Activities of daily living (subscale of the Friedreich's Ataxia Rating Scale [FARS])
- Clinician and patient global impressions of improvement
- Safety and tolerability of MIN-102 for up to 48 weeks of treatment and 4 weeks after discontinuation by assessment of AEs, vital signs, 12-lead ECG, echocardiogram, clinical laboratory tests, and palatability.

3.1.3 Exploratory Objectives

The exploratory objectives of the study are to evaluate the effect of 48 weeks of treatment with MIN-102 compared to placebo on the following:

- Change in the pre-treatment versus post-treatment slope of the SARA
- Neurophysiological parameters as assessed by motor evoked potentials (MEP) as an optional assessment
- Biochemical parameters in plasma: adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells and additional panel of biomarkers related to neurodegeneration and neuroinflammation
- Biochemical parameters in CSF (optional): adiponectin, neurofilament light chain adiponectin, Fatty acid binding protein 4 and additional panel of biomarkers related to neurodegeneration and neuroinflammation
- Volume of further specific brain regions
- DTI parameters, including fractional anisotropy, mean, axial, and radial diffusivity, in specific brain regions

3.1.4 Pharmacokinetic Objectives

Pharmacokinetic objective is to determine MIN-102 and M3 concentrations in plasma.

3.2 Study Design

Eligible subjects will be randomized to treatment for 48 weeks with MIN-102 or placebo in a 2:1 ratio after obtaining written informed consent from the subject or, if the subject is a minor, obtaining written informed consent from a parent/legal guardian and written assent from the subject, completion of all screening evaluations within 28 days (4 weeks), and confirmation that the subject has met all inclusion criteria and none of the exclusion criteria.

Motor Evoked Potentials and cerebrospinal fluid sampling are optional and require separate informed consent and assent.

The Screening visit (V-1) occurs after written informed consent is obtained. After the Screening visit, eligible subjects fulfilling all the inclusion and none of the exclusion criteria will be scheduled for a Baseline visit (V0) within a maximum of 28 days after the Screening visit (V-1) and will be randomized to receive an individualized starting dose of MIN-102 or placebo. Subjects will be instructed to take a daily dose of the study treatment at approximately the same time in the morning throughout the entire treatment phase. The administered dose of MIN-102 is intended to achieve a target exposure of 170 µg.hr.mL-1.

In addition to the Screening visit (V-1) and Baseline visit (V0), subjects will be evaluated at two interim safety visits (ISVs) occurring 2 and 8 weeks after V0 (ISV1 and ISV2), and at 4 (V1), 12 (V2), 24 (V3), 36 (V4), and 48 (V5) weeks after V0.

ISV1 and ISV2 may occur at home, all other visits will be performed on-site. The home visits will be performed by an accredited nurse who is certified in Good Clinical Practice (GCP). Results of all scheduled assessments will be made available to the investigator as soon as possible.

Baseline evaluations will consist of assessments for safety (ECGs, Labs) and tolerability, imaging evaluations (MRI/MRS), evaluations of clinical status on SARA, global clinical

rating scales, MEP (optional), and patient questionnaires. Assessment of biochemical markers in plasma and CSF (optional) and blood sampling for plasma levels of MIN-102.

Post-baseline evaluations will consist of assessments for safety (ECGs, Echocardiograms, Labs) and tolerability and blood sampling for plasma levels of MIN-102 at all scheduled on-site visits (except for ISV1 and ISV2), imaging evaluations at V3 and V5, assessment of biochemical markers in plasma at V2, V3 and V5, assessment of biochemical markers in CSF at V3 and V5 (optional), evaluations of clinical status on SARA, global clinical rating scales, MEP (optional), and patient questionnaires at V3 and V5. All assessments for safety, tolerability, and biochemical markers in plasma will also be performed at premature discontinuation.

There will also be regularly scheduled phone calls to the subjects at 6, 10, 16, 20, 28, 32, 40, and 44 weeks after V0. During these calls, the site will ask the subject for changes in concomitant medications and AEs, in particular for symptoms possibly indicative of cardiac failure.

An individualized dose based on PBPK will be chosen to yield a geometric mean AUC_t of approximately 170 µg.hr/mL (± 20%). Blood sampling to determine MIN-102 plasma concentrations will occur before the first dose, and then at each scheduled visit (except ISV1 and ISV2) immediately before each daily dose. The observed plasma concentrations of MIN-102 at V1 will be used to guide dose adjustments. After a potential dose adjustment following PK results from V1, no further dose adjustments are allowed, except for dose reductions to manage safety or tolerability issues (see sections 3.4.3 and 3.4.4 of protocol for further details)

Individual downward adjustments of the dose at any time point after V0 may be implemented by the investigator for safety/tolerability reasons; however, the minimum permitted dose in terms of corresponding volume rounded to the nearest 0.5 mL will be individually calculated for each subject to achieve a plasma exposure of ≥100 µg.hr/mL.

A FUV will occur 4 weeks after last dose of study drug.

3.2.1 Visits and Assessments

Table 1 presents the schedule of assessments for the study. This section describes the study evaluations by visit.

Table 1: Flow Chart of Study Procedures

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Informed consent[11]	X														
Assignment of subject identification number	X														
Inclusion & exclusion criteria	X	X[2]													
Medical history/concomitant disease	X	X[2]													
Demographics	X														
Previous medication	X	X[2]													
Physical examination	X		X[7]	X[7]		X[7]		X		X		X		X	X

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Vital signs (height, body weight, blood pressure, pulse rate, temperature)[3]	X	X	X	X		X		X		X		X		X	X
Echocardiogram	X			X				X		X		X		X	X
Hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody	X														
Hba1c	X													X	X
Pregnancy test[12]	X	X		X		X		X	X	X	X	X	X	X	X

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Laboratory safety tests (haematology, blood chemistry, prothrombin time, NTpro BNP, urinalysis including cytology)[4]	X	X		X				X		X		X		X	X
Randomization[5]		X													
Biomarker blood sampling[6]		X						X		X				X	
Biomarker CSF sampling (optional)[6]		X								X				X	
Blood sampling (MIN-102 and M3 levels)[6]		X		X				X		X		X		X	
Subject diary review			X	X		X		X		X		X		X	
Study drug and study diary dispensation		X						X		X		X			

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Study drug accountability								X		X		X		X	
Palatability assessment[10]		X		X				X		X		X			
12-lead ECG (in triplicate)	X	X[8]		X[8]				X[8]		X[8]		X[8]		X	X
SARA	X	X								X				X	
CCFS		X								X				X	
MRI/MRS		X								X				X	
MEP (optional)		X								X				X	
CGI-S		X								X				X	
CGI-I										X				X	
PGI-I										X				X	
FSS		X								X				X	
EQ-5D-5L		X								X				X	
Activities of Daily Living subscale of FARS		X								X				X	
Adverse event recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Screening (V-1)	Baseline (V0)	ISV1[9]	V1	Phone call 1	ISV2[9]	Phone call 2	V2	Phone calls 3/4	V3	Phone calls 5/6	V4	Phone calls 7/8	V5 (EOT[13])	FUV
Timing (weeks)	**Up to 28 days prior to Baseline**	**0**	**2 (±3 days)**	**4 (±3 days)**	**6 (±3 days)**	**8 (±3 days)**	**10 (±3 days)**	**12 (±5 days)**	**16/20 (±5 days)**	**24 (±5 days)**	**28/32 (±5 days)**	**36 (±5 days)**	**40/44 (±5 days)**	**48 (±5 days)**	**28[1] days (±5) after the last dose**
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

NTpro BNP = NT-proB-type natriuretic peptide; CCFS = cerebellar composite functional scale; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; CSF = cerebrospinal fluid; ECG = electrocardiogram; EOT=End of treatment; EQ-5D-5L = European Quality of Life 5 Dimensions; FARS = Friedreich's Ataxia Rating Scale FSS = Fatigue Severity Scale; FUV = follow up visit; ISV = interim safety visit; MEP = motor evoked potentials; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PGI-I = Patient Global Impression – Improvement; SARA = Scale for the Assessment and Rating of Ataxia; V = visit

[1] To be performed for all subjects, including those who discontinue prematurely
[2] Confirmation of screening information
[3] All assessments at V0 and later are performed immediately prior to study medication administration. Temperature measurements will only be performed at V0, V5 and FUV, and height only at screening (V-1).
[4] Samples are collected pre-dose at the same time as pharmacokinetic samples, in the morning under fasted conditions.
[5] After all entry criteria are confirmed
[6] Pre-dose
[7] Only examination for peripheral edema
[8] At the Baseline visit (V0) ECGs will be recorded pre-dose and approximately 3 hours post-dose. At visits from V1-V4 they will be recorded at approximately 3 hours post-dose.
[9] Clinic or home visit
[10] Immediately after administration of daily dose
[11] If subject becomes 18 years old during the study, signature of the adult ICF will be required.
[12] Female patients of childbearing potential will have a serum pregnancy test within 7 days before the first study drug administration. If the Screening Visit has been performed > 7 days before the Baseline Visit, a home nurse visit may be scheduled to perform the serum test. At Screening a serum pregnancy test will be performed. At Baseline and FUV a urine and serum pregnancy test will be performed. All the remaining visits (monthly) urine pregnancy test

3.3 Sample Size Justification

This is a phase 2a study without available data to support a formal power calculation, and therefore formal statistical significance is not sought.

Assuming an approximate drop-out rate of 15%, 36 eligible subjects will be enrolled and randomized in a 2:1 ratio to MIN-102 and placebo to achieve 30 evaluable subjects.

4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.4 or higher). Figures may be prepared using R software (version 3.5.0 or later).

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, first and third quartiles, minimum and maximum values.

The tables will be created by treatment arm. Listings with individual values will be provided for all data presented in the tables.

4.1 Study Period and Visit Window Definitions

4.1.1 Study Periods

Screening period will be defined as the period before the date of first placebo or MIN-102 administration.

Treatment period will be defined as the period between the date of first placebo or MIN-102 administration and the latest of date for last placebo or MIN-102 administration and end of treatment visit.

Follow-up period will be defined as the period between the date of last IMP administration and the date of the follow up visit.

4.1.2 Visit Windows

Visit windows are defined in the protocol. Those will not be used in the analysis to avoid excluding important data due to dates outside visit windows. Tables will assume that observations are from the recorded visit irrespective of the date specified.

4.2 Planned analyses

The final analysis will be performed when the trial is completed, and the database is locked.

4.3 Definition of Populations

4.3.1 Modified Intention-To-Treat (mITT) Population

The modified Intention-To-Treat population (mITT) will consist of all subjects who took at least 1 dose (partial or complete) of study drug and had at least 1 post-baseline spinal cord area cervical segment C2-C3 measurement and SARA assessment at the same visit.

This is the primary population for the primary efficacy analysis.

4.3.2 Per Protocol (PP) Population

The Per Protocol population (PP) consists of all subjects in the mITT analysis set without a major protocol deviation.

4.3.3 Safety Population

The Safety population will include all subjects who took at least 1 dose (partial or complete) of study drug.

4.4 Treatment Assignment and Treatment Arms

The subject identification number will be used to identify the subject throughout the study and will be recorded in the electronic case report form. This number must not be re-used. If the full screening visit needs to be repeated, subjects will be screen failed in IRT. A new subject identification number from IRT will be assigned to the subject, to avoid confusion with data from the previous screening. If the full screening visit is not repeated, the subject will keep the same identification number.

Subjects will be randomized using IRT. The assignment to MIN-102 or placebo will be made by a dynamic minimization procedure in a 2:1 ratio using the following factors: site.

The dynamic minimization will use a stochastic treatment allocation algorithm based on the variance method. No treatment allocation will be deterministic.

Randomization data will be kept strictly confidential and accessible only to authorized persons until the time of unblinding after locking the database upon completion. Only after the study is completed and the data is verified and locked will the randomization codes be made available for data analysis.

4.5 Calculated Variables

- Study day 1 is defined as the first day when study treatment was received.
- The baseline is defined as the last assessment done before or on study day 1. Assessments done on the date of study treatment administration are assumed to take place before the administration, unless specified otherwise.
- Change from baseline is defined as the post-baseline value – baseline value.
- Percent change from baseline is defined as 100*(post-baseline value – baseline value)/baseline value. If the baseline value is 0 and the post-baseline value is 0, the change from baseline and the percent change from baseline are both 0. If the baseline value is 0 and the post-baseline value is not 0, the change from baseline is the same as the post-baseline value and the percent change from baseline will be missing.
- The age will be calculated as number of years between the date of randomization and the date of birth, rounded down.
- The duration of treatment in days will be calculated by computing [(the number of days between the end date of IMP and the date of first dose) + 1 day], with the end date of IMP defined as date of last IMP dose or, if missing, the oldest date among: last contact date, the date of death or the cut-off date.
- Compliance (%) = Cumulative dose (mL)/Planned (i.e. as prescribed by investigator) cumulative dose (mL)

- Cumulative dose (mL) = (Number of kits dispensed x 1500 mL) – Total volume returned (mL).
- Planned (i.e. as prescribed by investigator) cumulative dose (mL) = sum [(end date of IMP – start date IMP + 1) x planned (i.e. as prescribed by investigator) volume [mL]] for each different planned volume.
- AUC_{0-24} of MIN-102 will be extrapolated from Cmin values using the following algorithm: AUC_{0-24} = (Cmin + 1104.1) / 0.0341
- Metabolic ratio (M) for each sample where both M3 and MIN-102 are analyzed will be estimated using formula: M3 Cmin/MIN-102 Cmin

4.6 Partial Dates

Partial or missing dates in general will not be imputed.

For the assignment to prior or concomitant medication the following rules will be applied in case of incomplete or missing dates:

- If end date is missing, the end date will be set to the last contact date.
- If end date is incomplete: if the day is missing: the end date will be imputed with the last day of the month; if the day and month are missing: the end date will be imputed with min (31 December of the year, last contact date, date of death).
- If start date is missing: if end date is before the date of first IMP administration, the start date will remain missing; if end date is after or on the date of first IMP administration or the medication is ongoing, the start date will be imputed by the date of first IMP administration.
- If start date is incomplete: if end date is before the date of first IMP administration, the start date will remain incomplete; if end date is after or on the date of first IMP administration or the medication is ongoing, if the day is missing: the start date will be imputed with the last day of the month; if the day and month are missing: the start date will be imputed with 31 December of the year.

The imputed dates will only be used for the assignment to prior or concomitant and will not be used in any other calculation and will not be listed.

For the assignment of adverse events (AE) the following rules will be applied in case of missing start date:

- if end date is before the date of first IMP administration, the start date will remain missing (medical history);
- If start date is missing and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed by the date of first IMP administration (AE).
- If start date is incomplete and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed as follows: if the day is missing then the start date will be imputed with the last day of the month; if the day and month are missing then the start date will be imputed with minimum of (31 December of the year and the AE end date) (AE).

The imputed date will only be used for the assignment to adverse event and will not be used in any other calculation and will not be listed.

4.7 Methods To Be Used For Handling Missing Data

All available data will be included in data listings and tabulations.

No imputation of missing data is planned for safety and efficacy endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

4.8 Changes to Protocol

The following changes from protocol have been implemented in this document:

- Efficacy analyses initially planned at 48 weeks visit are repeated at 24 weeks visit;
- Sensitivity analysis of primary efficacy endpoint by means of mixed model with repeated measures has been added;
- Exploratory analyses of spinal cord area cervical segment C2-C3 [mm^2] (primary endpoint) and SARA total score for 2 subsets of patients have been added;
- Exploratory analyses of spinal cord area cervical segment C2-C3 [mm^2] estimated from spine T2 image have been added;
- The secondary endpoint "Diffusion tensor imaging fractional anisotropy, mean, radial and axial diffusivity cervical segments C2-C7 [10^{-3} mm^2/s]" has been corrected to "Diffusion tensor imaging fractional anisotropy, mean, radial and axial diffusivity cervical segments C2-C6 [mm^2/s]";
- Analysis of CGI-I and PGI-I (secondary efficacy endpoint) where the 7 categories of scale are grouped as 3 categories has been added.
- Update of the prior SARA slope definition (see section 8.3.2): The analysis will include all patients with at least two assessments performed ≥20 weeks prior to randomization and with an interval of time between them of at least 5 months and at most 15 months, provided that the point closer to randomization is not farther than 15 months. The SARA assessment at Screening will serve as the last datapoint to calculate decline prior to treatment. Similarly, the slope of SARA scale on treatment will be calculated using the SARA assessments at visits V0, V3, and V5.

5. Study Patients

5.1 Disposition of Patients

The number of patients in each population will be tabulated by treatment arm as defined in section 4.4 and overall. The number of screened patients will be presented in the table of patient disposition.

The frequency of patients treated, of patients who discontinued the study treatment and of patients who discontinued the follow-up visit will be given by treatment arm and overall for the safety population. The primary reason for discontinuation of the study treatment and discontinuation the follow-up visit will be summarized. The details of the 'other reason' will be included in the listing.

Reason for screening failure will be summarized by treatment arm and overall. The details of the 'other reason' will be included in the listing.

5.2 Protocol Deviations

The major protocol deviations as well as deviations related to COVID-19 will be summarized for each treatment arm and overall for the safety population. The details will be listed by patient and treatment arm.

Violations of inclusion and/or non-inclusion criteria, intake of forbidden concomitant medications and deviations of other restrictions will be considered in the determination of the major deviations.

Protocol deviations will be defined as major or minor by the Sponsor before the final database locks.

5.3 In- and Exclusion Criteria

Listing of all in- and exclusion criteria not met will be provided.

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to patient characteristics at baseline will be displayed for the safety population(s).

The variables to be summarized are:

- Gender
- Age at date of informed consent
- Age group (at date of informed consent): from 12 to 17 y.o., older than 17 y.o.
- Age at onset of symptoms
- Height
- Weight
- Race
- Ethnicity
- Time since genetic diagnosis
- Time since onset of symptoms

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) and tabulated by system organ class and preferred term by treatment arm and overall for the safety population.

Stratification information (i.e. site) will be tabulated by treatment arm.

7. Prior and Concomitant Treatment and Procedures

Prior and concomitant medications will be classified according to World Health Organization Drug Dictionary (WHO-DD Version v 2019 v1).

The number and percentage of participants receiving a prior as well as a concomitant medication will be displayed by anatomical main group (1st level of the Anatomical Therapeutical Chemical –ATC- classification) and chemical subgroup (4th level of the ATC classification) by treatment arm and overall for the safety population.

Medications will be reported as prior when they start and end before the first day of study treatment.

Medications will be reported as concomitant when they start before, on or after first day of study treatment and continue afterwards.

Prior and concomitant medication summaries will be sorted alphabetically by anatomical main group and chemical subgroup.

A listing of all medications recorded on the prior and concomitant medications CRF page will provide details including indication, dose, route, frequency, and start and end dates.

Concomitant procedures and surgeries will be tabulated by system organ class and preferred term by treatment arm and overall for the safety population. These will be sorted alphabetically by system organ class and preferred term. A listing of concomitant procedures and surgeries will be produced by treatment arm.

8. Efficacy Evaluation

All the efficacy analyses will be performed on the mITT and the Per-Protocol (PP) populations unless otherwise stated.

8.1 Primary Evaluation

The primary endpoint for this study is the change from baseline in spinal cord area cervical segment C2-C3 [mm^2] estimated from brain T1 image after 48 weeks of treatment.

Descriptive statistics for spinal cord area cervical segment C2-C3 [mm^2] estimated from brain T1 image will be presented at baseline, at 24 weeks and at 48 weeks by treatment arm and overall. Descriptive statistics for change from baseline in spinal cord area cervical segment C2-C3 [mm^2] estimated from brain T1 image at 24 weeks and 48 weeks will be presented similarly. Box plots of spinal cord area cervical segment C2-C3 [mm^2] estimated from brain T1 image as well as change from baseline will also be displayed over time by treatment arm. Graphs of individual patient spinal cord area cervical segment C2-C3 [mm^2] estimated from brain T1 image over time will also be displayed by treatment arm.

Statistical analysis will be based on an analysis of covariance (ANCOVA) model for change from baseline at 24 weeks and 48 weeks with treatment arm as a fixed effect and the baseline value as a covariate. The least squares means along with their 95% confidence interval will be calculated as well as the associated p-value for difference in those means. Here is an example of SAS code that will be used to fit the ANCOVA model:

```
PROC GLM data=xxxx;
  CLASS treatment;
  MODEL change = treatment base / solution;
RUN;
```

With:

- treatment = Treatment arm;
- change = Change from baseline in spinal cord area cervical segment C2-C3 [mm^2] at 24 weeks, at 48 weeks whichever applies;
- base = Baseline value of spinal cord area cervical segment C2-C3 [mm^2].

A mixed model with repeated measures on the change from baseline as dependent variable will be performed as a sensitivity analysis. Baseline, treatment and visit will be considered as independent variables. This model has two assets:

1) it doesn't exclude patients with no measure at week 48

2) it takes into account the values at week 24 as it is a repeated measure model.

Here is an example of SAS code that will be used to fit the mixed model with repeated measures:

```
PROC MIXED data=xxxx method=reml;
  CLASS treatment visit patid;
  MODEL change = treatment base visit treatment*visit / ddfm=kenwardroger solution;
  REPEATED visit / subject=patid type=un;
RUN;
```

With:

- treatment = Treatment arm;
- visit = Scheduled visit time (24 weeks and 48 weeks);
- patid = Patient identifier;
- change = Change from baseline in spinal cord area cervical segment C2-C3 [mm^2] at visit;

- base = Baseline value of spinal cord area cervical segment C2-C3 [mm²].

In this study, formal statistical significance on individual endpoints is not sought. The study will look for clinically meaningful effects based on point estimates and 95% confidence intervals and the p-values will only be used as a guide to activity.

Descriptive statistics, ANCOVA and mixed model with repeated measures, box plots of actual values and change from baseline in spinal cord area cervical segment C2-C3 [mm²] estimated from brain T1 image as well as graphs of individual patient data over time will be repeated, in an exploratory intent, for the following subsets based on treatment arm and dose of study drug prescribed by the investigator between Visit 1 (Week 4) and Visit 5 (Week 48) or early termination:

- Subset "Placebo" includes all subjects randomized to Placebo.
- Subset "MIN-102 dose as recommended" includes all subjects randomized to MIN-102 to whom the investigator prescribed the same dose (±10%) as the dose recommended by the PK expert for at least 50% of days between V1 and V5.
- Subset "MIN-102 dose reduced" includes all subjects randomized to MIN-102 to whom the investigator prescribed a dose that was >10% to ≤40% lower than the dose recommended by the PK expert for at least 50% of days between V1 and V5.

Further exploratory subsets may be added as deemed necessary.

The following comparisons will be conducted by means of above mentioned ANCOVA and mixed model with repeated measures:

- Subset "MIN-102 dose as recommended" versus subset "Placebo"
- Subset "MIN-102 dose reduced" versus subset "Placebo"
- Subset "MIN-102 dose as recommended" versus subset "MIN-102 dose reduced"

These exploratory analyses will be based on post-baseline data and as such will be interpreted cautiously. Here are example of SAS codes that will be used to fit the ANCOVA and mixed model with repeated measures:

```
PROC GLM data=xxxx;
  CLASS subset;
  MODEL change = subset base / solution;
RUN;
```

```
PROC MIXED data=xxxx method=reml;
  CLASS subset visit patid;
  MODEL change = subset base visit subset*visit / ddfm=kenwardroger solution;
  REPEATED visit / subject=patid type=un;
RUN;
```

With:

- subset = subset as described above;
- visit = Scheduled visit time (24 weeks and 48 weeks);
- patid = Patient identifier;
- change = Change from baseline in spinal cord area cervical segment C2-C3 [mm²] at visit;
- base = Baseline value of spinal cord area cervical segment C2-C3 [mm²].

In addition, exploratory analyses of spinal cord area cervical segment C2-C3 [mm²] estimated from spine T2 image will be conducted. Descriptive statistics for spinal cord area cervical segment C2-C3 [mm²] estimated from spine T2 image as well as change from baseline will be presented at baseline, at 24 weeks and at 48 weeks by treatment arm and overall. Box plots of spinal cord area cervical segment C2-C3 [mm²] estimated from spine T2 image as well as change from baseline will also be displayed over time by treatment arm. Graphs of individual patient spinal cord area cervical segment C2-C3 [mm²]

estimated from spine T2 image over time will also be displayed by treatment arm. An analysis of covariance (ANCOVA) model for change from baseline at 24 weeks and 48 weeks with treatment arm as a fixed effect and the baseline value as a covariate will be performed as well as a mixed model with repeated measures on the change from baseline as sensitivity analysis.

8.2 Secondary Evaluation

8.2.1 Secondary endpoints with both baseline and post-baseline measurements

Descriptive statistics for the below listed endpoints will be presented by visits (baseline included) and treatment arm. The change from baseline at 24 and 48 weeks will be presented similarly.

- Scale for Assessment and Rating of Ataxia (SARA) total score
- Diffusion tensor imaging: fractional anisotropy, mean, radial and axial diffusivity at cervical segments C2-C6 [mm^2/s]
- Magnetic resonance spectroscopy tNAA/mIns ratio in spinal cord
- MRI quantitative susceptibility mapping (QSM) for iron concentration [ppb]
- Dentate nuclei volume [mm^3]
- Fixel-based analyses of the brain including FD, FC and FDC
- Cerebellar Composite Functional Scale (CCFS)
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- Fatigue Severity Scale (FSS)
- Activities of Daily Living (subscale of the Friedreich's Ataxia Rating Scale [FARS])
- Global Impression Scales – Severity (CGI-S)

Box plots and graphs of individual patient data over time for the following parameters will also be displayed by treatment arm:

- Scale for Assessment and Rating of Ataxia (SARA) total score
- Diffusion tensor imaging: mean, radial and axial diffusivity at cervical segments C2-C6 [mm^2/s]
- Magnetic resonance spectroscopy tNAA/mIns ratio in spinal cord
- MRI quantitative susceptibility mapping (QSM) for iron concentration [ppb]
- Dentate nuclei volume [mm^3]
- Fixel-based analyses of the brain: FD and FDC in posterior limb of internal capsule

Summary statistics in the form of least squares means will be based on analysis of covariance (ANCOVA) models at 24 weeks and 48 weeks with treatment arm as a fixed effect and the baseline value as a covariate. In this study, formal statistical significance on the individual endpoints is not sought. The study will look for clinically meaningful effects based on point estimates and 95% confidence intervals and p-values will only be used as a guide to activity. Here is an example of SAS code that will be used to fit the ANCOVA model:

```
PROC GLM data=xxxx;
  CLASS treatment;
  MODEL change = treatment base / solution;
RUN;
```

With:

- treatment = Treatment arm;
- change = Change from baseline in endpoint at 24 weeks, at 48 weeks whichever applies;
- base = Baseline value of endpoint.

In addition, descriptive statistics, box plots and graphs of individual patient data over time as well as ANCOVA model for Scale for Assessment and Rating of Ataxia (SARA) total score will be repeated, in an exploratory intent, for the following subsets based on treatment arm and dose of study drug prescribed by the investigator between Visit 1 (Week 4) and Visit 5 (Week 48) or early termination:

- Subset "Placebo" includes all subjects randomized to Placebo.
- Subset "MIN-102 dose as recommended" includes all subjects randomized to MIN-102 to whom the investigator prescribed the same dose (±10%) as the dose recommended by the PK expert for at least 50% of days between V1 and V5.
- Subset "MIN-102 dose reduced" includes all subjects randomized to MIN-102 to whom the investigator prescribed a dose that was >10% to ≤40% lower than the dose recommended by the PK expert for at least 50% of days between V1 and V5.

Further exploratory subsets may be added as deemed necessary.

The following comparisons will be conducted by means of above mentioned ANCOVA and mixed model with repeated measures:

- Subset "MIN-102 dose as recommended" versus subset "Placebo"
- Subset "MIN-102 dose reduced" versus subset "Placebo"
- Subset "MIN-102 dose as recommended" versus subset "MIN-102 dose reduced"

These exploratory analyses will be based on post-baseline data and as such will be interpreted cautiously. Here is an example of SAS code that will be used to fit the ANCOVA model:

```
PROC GLM data=xxxx;
  CLASS subset;
  MODEL change = subset base / solution;
RUN;
```

With:

- subset = subset as described above;
- change = Change from baseline in spinal cord area cervical segment C2-C3 [mm²] at visit;
- base = Baseline value of spinal cord area cervical segment C2-C3 [mm²].

8.2.2 CGI-I and PGI-I

Clinician and patient global impression scales of improvement (CGI-I and PGI-I) are only measured at post-baseline visits. Descriptive statistics will be presented at 24 and 48 weeks by treatment arm and overall. Shift tables of CGI-I and PGI-I at 24 weeks versus at 48 weeks will also be created.

T-tests will be used to compare the two treatment arms. Formal statistical significance is not anticipated and the focus for interpretation will be the effect sizes.

In addition, CGI-I and PGI-I scales will be presented grouped as 3 categories: worsening (scores of 'minimally worse', 'much worse' and 'very much worse'), no change and improvement (scores of 'minimally improved', 'much improved' and 'very much improved'). Number and percentage of subjects as well as 95% confidence intervals for binomial proportions will be presented for each category by treatment arm and overall. Fisher's exact tests will be used to compare treatment arms for each category in an explorative intent.

8.2.3 Palatability

Descriptive statistics for palatability will be summarized over time by treatment arm and overall for the safety population.

8.3 Exploratory Evaluation

8.3.1 O'Brien composite variable

The sum of ranks of the change from baseline in spinal cord area and of the change from baseline in SARA total score will be combined in a composite variable at 24 and 48 weeks. Descriptive statistics for rank of the change from baseline in spinal cord area, rank of the change from baseline in SARA total score and the O'Brien composite variable will be summarized at 24 and 48 weeks by treatment arm and overall. This composite variable at 24 and 48 weeks will also be integrated in a rank analysis following the O'Brien procedure (O'Brien 1984). Graphical presentations of rank of the change from baseline in spinal cord area, rank of the change from baseline in SARA total score and O'Brien composite individual values over time as well as change from baseline in spinal cord area vs. change from baseline in SARA total score at 24 and 48 weeks will also be included.

8.3.2 Decline in SARA scale prior to randomization and on treatment

Analysis of decline in SARA scale prior to randomization and on treatment will be primarily conducted in a subset of patients who had at least two SARA assessments prior to screening and provided separate informed consent to allow using these data, for the mITT and PP populations. On a second hand, decline in SARA scale on treatment will be analyzed in all patients for the mITT and PP populations.

SARA slope prior to randomization will be calculated in those patients who provided separate informed consent. On-treatment SARA slope will be calculated in the subset of patients who have consented to using SARA data obtained prior to screening, and in all patients.

The slope of SARA scale prior to randomization will be estimated by means of linear regression model on all available previous SARA assessments taken prior to randomization. The analysis will include all patients with at least two assessments performed ≥20 weeks prior to randomization and with an interval of time between them of at least 5 months and at most 15 months, provided that the point closer to randomization is not farther than 15 months. The SARA assessment at Screening will serve

as the last datapoint to calculate decline prior to treatment. Similarly, the slope of SARA scale on treatment will be calculated using the SARA assessments at visits V0, V3, and V5.

The slope prior to randomization, the slope on treatment, the difference and the ratio between the slopes prior to randomization and on treatment will be computed for each patient.

For the analysis in the subset of patients who provided separate informed consent, a table with descriptive statistics will summarize the distribution of the slope prior to randomization, the slope on treatment, the difference of the slopes, and the ratio of the slopes. An analysis will be performed to compare the difference between the slope prior to randomization and the slope on treatment within each treatment arm. Furthermore, another analysis of covariance (ANCOVA) of the slope on treatment, the difference of the slopes and the ratio of the slopes of SARA scale taking into account decline prior to randomization will be used to compare treatment arms, in those patients who provided separate informed consent. Here is an example of SAS code that will be used to fit the ANCOVA model:

PROC GLM data=xxxx;

CLASS treatment;

MODEL variable = treatment slope_scr / solution;

RUN;

With:

treatment = Treatment arm;

variable = Slope on treatment, difference of the slopes and the ratio of the slopes of SARA scale ;

slope_scr = Slope prior to randomization.

For the analysis in all patients, a table with descriptive statistics will summarize the distribution of the slope on treatment separately for the subset of patients who provided separate informed consent, for all other patients and overall.

In addition, a graph will show changes on the decline of SARA scale for each individual patient.

8.3.3 Other exploratory objectives

Descriptive statistics for actual values and change from baseline over time by treatment arm and overall will be presented for the following exploratory parameters. These parameters will be evaluated separately and results will be appended to the CSR.

- Neurophysiological parameters as assessed by motor evoked potentials (MEP): amplitude after cervical stimulation, amplitude after central stimulation, cervical latency, mean central conduction time, MEP duration
- Biochemical parameters in plasma: adiponectin, neurofilament light chain, gene expression of frataxin, PGC-1α, NRF1, TFAM in peripheral blood mononuclear cells; additional panel of biomarkers related to neurodegeneration and neuroinflammation may be added
- Biochemical parameters in CSF: adiponectin, neurofilament light chain, fatty acid binding protein 4; additional panel of biomarkers related to neurodegeneration and neuroinflammation may be added

- Volume of further specific brain regions: medulla, pons, midbrain, thalamus, 3rd ventricle, 4th ventricle, caudate, putamen and cerebellum
- DTI parameters, including fractional anisotropy, mean, axial, and radial diffusivity, in specific brain regions: superior cerebellar peduncle; inferior cerebellar peduncle, posterior limb of internal capsule

Box plots and graphs of individual patient data over time for the following parameters will also be displayed by treatment arm:

- Volume of further specific brain regions: 3rd and 4th ventricle
- DTI parameters: mean and radial diffusivity in posterior limb of internal capsule

Analysis of covariance (ANCOVA) models at 48 weeks with treatment arm as a fixed effect and the baseline value as a covariate will also be conducted in an explorative intent. Here is an example of SAS code that will be used to fit the ANCOVA model:

```
PROC GLM data=xxxx;
  CLASS treatment;
  MODEL change = treatment base / solution;
RUN;
```

With:

- treatment = Treatment arm;
- change = Change from baseline in endpoint at 48 weeks;
- base = Baseline value of endpoint.

9. Safety Evaluation

All the safety analyses will be performed on the safety population.

9.1 Extent of Exposure

Duration of treatment [days] will be summarized by treatment arm and overall. Frequencies and reasons for change in dose prescribed by the investigator any time post-baseline and at each post-baseline visit will be summarized by treatment arm and overall. Number and percentage of patients who were prescribed by investigator a dose as recommended by PK expert (±10%) for at least 50% of days between V1 and V5 as well as of patients who were prescribed by investigator a dose reduced from >10% to ≤40% compared to the dose recommended by the PK expert for at least 50% of days between V1 and V5 will be summarized by treatment arm and overall.

Frequencies and reasons for change in dose taken by patient compared to dose prescribed by the investigator will also be summarized by treatment arm and overall. Additionally, compliance (%) over the whole treatment duration will be summarized descriptively by treatment arm and overall.

A listing of PK expert recommendation, planned and actual doses as well as compliance and drug accountability information will be provided by treatment arm.

9.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) and will be graded according to the National Center Institute Common Terminology Criteria for AEs (NCI-CTCAE criteria [v5.0]). Adverse events will be analyzed in terms of their type, incidence, severity (as described in protocol section 6.1.1.4) and relationship to the study treatment. Related AEs are defined as events with a relationship to study treatment reported as 'related' or 'not assessable'. Treatment-

emergent Adverse Events (TEAEs) are defined as AEs occurring on or after the first dose of study treatment. Missing or partial AE start date will be estimated in order to include events in summary tables in case of doubt (see section 4.6 for more details).

A summary table will present the number and percentage of patients by treatment arm and overall with at least one:

- Treatment emergent adverse event
- Treatment emergent adverse event related to study treatment
- Treatment emergent adverse event with a relationship to study treatment reported as 'related'
- Treatment emergent adverse event with a relationship to study treatment reported as 'not assessable'
- Serious adverse event
- Serious adverse event related to study treatment
- Grade 3 or 4 treatment emergent adverse event
- Grade 3 or 4 treatment emergent adverse event related to study treatment
- Treatment emergent adverse event leading to drug withdrawal
- Treatment emergent adverse event leading to drug interruption
- Treatment emergent adverse event leading to dose reduction
- Adverse event leading to death (Grade 5)
- Related adverse event leading to death (Grade 5)

In addition, tabulations of the number of patients who experienced TEAEs will be presented by system organ class and preferred term. Patients will only be counted once for each preferred term. In case a patient experienced the same event more than once, the worst severity will be presented.

The following tabulations will be presented:

- Treatment emergent adverse events
- Treatment emergent adverse events related to the study treatment
- Treatment emergent adverse event with a relationship to study treatment reported as 'related'
- Treatment emergent adverse event with a relationship to study treatment reported as 'not assessable'
- Treatment emergent adverse events leading to drug withdrawal
- Serious adverse events
- Grade 3 or 4 treatment emergent adverse events
- Adverse events with fatal outcome

Listings of all adverse events by treatment arm will be provided, flagging the ones that are treatment emergent, including the patient identifier, age, race, sex, verbatim, preferred term, duration of the event, severity, action taken, outcome, causality, and date of onset.

9.3 Deaths and Serious Adverse Events

Serious adverse events (SAEs), fatal AEs and NCI-CTCAE grade 3 or 4 toxicities will be summarized grouped by system organ class and preferred term and listed as described above.

In addition, the number of deaths will be tabulated by treatment arm and overall.

9.4 Clinical Laboratory Determination

The following laboratory parameters will be displayed:

- **Blood chemistry**: total bilirubin, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, creatinine, urea, uric acid, cholesterol, triglycerides, total protein, albumin, NT-proBNP, glucose, inorganic phosphate, sodium, potassium, calcium, chloride, and bicarbonate (at all visits)
- **Prothrombin time**
- **Hematology**: HbA1c (only at V-1, V5, and follow up), leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, lymphocytes, monocytes, eosinophils, basophils, neutrophils, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- **Urinalysis** (qualitative): hemoglobin, urobilinogen, ketones, glucose, protein, bilirubin, leukocytes, pH, and nitrite
- **Cytological examination** for presence of abnormalities in bladder epithelial cells
- **Serology**: hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody (only at V-1).

Shift tables of grade at baseline versus worst post-baseline grade will be created for laboratory parameters that can be graded according to NCI-CTCAE [v5.0] by treatment arm and overall. Otherwise, shift tables of baseline versus worst post-baseline abnormality grade according to normal range will be produced by treatment arm and overall. The NCI-CTCAE grading of the laboratory parameters will only be based on laboratory values and not on any symptoms or concomitant medications.

The laboratory parameters which cannot be graded will be summarized descriptively by visit separately for each treatment arm and overall. The quantitative parameters will be described by the mean, the standard deviation, the median, the first and the third quartile and the range. The qualitative parameters will be described by displaying the frequency of patients corresponding to each level of the parameter.

For cytological examination, a shift table of baseline versus any time post-baseline Paris System Code for abnormality will also be produced by treatment arm and overall. Paris System Codes will be grouped according to the following categories:

Category	Code	Findings
Normal or non-significant other findings	1/ Code NCA	Insufficient urothelial cells, decaying cells remnants
	2/ Code NCC	Crystals obscuring urothelial cells
	3/ Code NCI	Excessive inflammatory cells obscuring urothelial cells
	4/ Code NCH	Excessive blood cells obscuring urothelial cells
	5/ Code NEG	Regular urothelial cells without significant nuclear atypia
Hyperplasia	6/ Code UHP	Regular urothelial cells and cohesive groups of urothelial cells without significant nuclear atypia. Urothelial hyperplasia
Polyomavirus	7/ Code UPV	Regular isolated or groups of urothelial cells without neoplastic atypia. Presence of isolated cells with changes associated with polyomavirus

Nuclear atypia	8/ Code UDC	Regular isolated or groups of urothelial cells without neoplastic atypia. Presence of dystrophic atypic cells
	9/ Code AUC	Presence of cells with nuclear atypia of undetermined significance
Malignancy	10/ Code SHG	Presence of few urothelial cells showing increased nuclear/cytoplasmic ratio with hyperchromasia and irregular chromatin and nuclear membranes. Suspicious for high-grade urothelial carcinoma (SHGUC)
	11/ Code HGU	Numerous abnormal cells with high nuclear/cytoplasmic ratio, hyperchromasia, coarse chromatin, nuclear membrane irregularity with focal thickness. High-grade urothelial carcinoma (HGUC)
	12/ Code LGN	Presence of some three-dimensional clusters of cells with mild cytologic atypia and fibrous tissue or capillary appreciated in the center. No high-grade atypia. Low-grade urothelial neoplasia (LGUN)

Number and percentage of patients will be summarized for the following shifts:

1. Normal or non-significant other findings (Codes 1-5) at baseline to hyperplasia (Code 6) any time post-baseline;
2. Normal or non-significant other findings (Codes 1-5) at baseline to nuclear atypia (Codes 8-9) any time post-baseline;
    a. Normal or non-significant other findings (Codes 1-5) at baseline to dystrophic atypic cells (Code 8) any time post-baseline;
    b. Normal or non-significant other findings (Codes 1-5) at baseline to nuclear atypia of undetermined significance (Code 9) any time post-baseline;
3. Normal or non-significant other findings (Codes 1-5), or hyperplasia (Code 6), or polyomavirus (Code 7), or nuclear atypia (Codes 8-9) at baseline to neoplasia (Codes 10-12) any time post-baseline;
    a. Normal or non-significant other findings (Codes 1-5), or hyperplasia (Code 6), or nuclear atypia (Codes 8-9) at baseline to suspicious for high-grade urothelial carcinoma (Code 10) any time post-baseline;
    b. Normal or non-significant other findings (Codes 1-5), or hyperplasia (Code 6), or nuclear atypia (Codes 8-9) at baseline to high-grade urothelial carcinoma (Code 11) any time post-baseline;
    c. Normal or non-significant other findings (Codes 1-5), or hyperplasia (Code 6), or nuclear atypia (Codes 8-9) at baseline to low-grade urothelial neoplasia (Code 12) any time post-baseline.

In addition, a graph will show the evolution of NT-proBNP over time for each patient separately for each treatment arm.

9.5 Vital Signs

Descriptive statistics for body weight, systolic and diastolic blood pressure, heart rate and body temperature will be presented by visit. Both absolute values and change from baseline (only for post-randomization periods) will be presented. Percent change from baseline will be added for summary of body weight. In case of multiple measurements by visit, the latest measurement will be used for baseline while the highest measurement will be used for post-baseline summary.

In addition, a graph will show the evolution of body weight over time for each patient separately for each treatment arm. Boxplots for body weight, change from baseline and percent change from baseline in body weight over time will also be produced by treatment arm.

9.6 ECG results and Cardiovascular Findings

Absolute values and change from baseline (only for post-randomization periods) in LVEF will be summarized descriptively over time by treatment arm and overall.

Absolute values, change from baseline to post-dose at visit (only for post-randomization periods) in heart rate, PR interval, RR interval, QRS duration, QT interval and QTcF interval will be summarized descriptively by visit, and timepoint when applicable, by treatment arm and overall. In case of multiple measurements by visit, the latest measurement, pre-dose when applicable, will be used for baseline while the highest measurement will be used for post-baseline summary.

Echocardiogram interpretation as well as 12-lead ECG evaluation will be summarized over time by treatment arm and overall. Shift tables of abnormality grade at baseline versus worst post-baseline grade will be produced for echocardiogram interpretation and 12-lead ECG evaluation will be reported at baseline and the worst post-baseline value will be reported. The worst post-baseline value is defined based on the following hierarchy: not assessed < normal < abnormal not clinically significant < abnormal clinically significant.

10. Pharmacokinetics

The PK parameters are MIN-102 and M3 Cmin, extrapolated AUC for MIN-102 and metabolic ratio.

The PK parameters will be summarized descriptively according to the following subsets and overall for the MIN-102 subjects in safety population separately by gender and age group (aged ≥ 12 to 17 y.o. and adults), and overall.

- Summary by visit: subsets will be based on MIN-102 dose prescribed by investigator over at least the 5 days before the corresponding visit:
    - Subset "MIN-102 dose as recommended at visit" includes all subjects randomized to MIN-102 to whom the investigator prescribed the same dose (±10%) as the dose recommended by the PK expert over at least the 5 days before the corresponding visit.
    - Subset "MIN-102 dose reduced at visit" includes all subjects randomized to MIN-102 to whom the investigator prescribed a dose that was >10% to ≤40% lower than the dose recommended by the PK expert over at least the 5 days before the corresponding visit.
- Summary of average value over all visits (Visit 1 to Visit 5): subsets will be based on MIN-102 dose prescribed by the investigator between Visit 1 (Week 4) and Visit 5 (Week 48) or early termination:
    - Subset "MIN-102 dose as recommended" includes all subjects randomized to MIN-102 to whom the investigator prescribed the same dose (±10%) as the dose recommended by the PK expert for at least 50% of days between V1 and V5.
    - Subset "MIN-102 dose reduced" includes all subjects randomized to MIN-102 to whom the investigator prescribed a dose that was >10% to ≤40% lower than the dose recommended by the PK expert for at least 50% of days between V1 and V5.

The following summary statistics will be included: number of observations (n), number of observations below lower limit of quantitation (LLOQ), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (%CV), median, range, and geometric mean, and geometric %CV. Geometric mean and geometric %CV will not be calculated if at least one value is below lower limit of quantitation (LLOQ). If more than 50% of values are below LLOQ at a given visit, SD and %CV will not be calculated.

11. References

O'Brien, P. C. (1984). "Procedures for comparing samples with multiple endpoints." Biometrics **40**(4): 1079-1087.

eTable 1 12-lead ECG Endpoint Interpretation and Echocardiogram Interpretation by Visit (Safety Population)

Assessment		Leriglitazone N = 26	Placebo N = 13	All N = 39
12-lead ECG Endpoint	Baseline, n (%)			
	n	26	13	39
	Normal	5 (19.2)	3 (23.1)	8 (20.5)
	Abnormal, not clinically significant	21 (80.8)	9 (69.2)	30 (76.9)
	Abnormal, clinically significant	0	1 (7.7)[a]	1 (2.6)
	Not assessable	0	0	0
	Week 0 (post-dose), n (%)			
	n	26	13	39
	Normal	3 (11.5)	4 (30.8)	7 (17.9)
	Abnormal, not clinically significant	23 (88.5)	8 (61.5)	31 (79.5)
	Abnormal, clinically significant	0	1 (7.7)	1 (2.6)
	Not assessable	0	0	0
	Week 4, n (%)			
	n	24	13	37
	Normal	1 (4.2)	4 (30.8)	5 (13.5)
	Abnormal, not clinically significant	23 (95.8)	9 (69.2)	32 (86.5)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0
	Week 12, n (%)			
	n	25	12	37
	Normal	3 (12.0)	2 (16.7)	5 (13.5)
	Abnormal, not clinically significant	22 (88.0)	10 (83.3)	32 (86.5)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0
	Week 24, n (%)			
	n	22	12	34

	Normal	3 (13.6)	3 (25.0)	6 (17.6)
	Abnormal, not clinically significant	18 (81.8)	9 (75.0)	27 (79.4)
	Abnormal, clinically significant	1 (4.5)[b]	0	1 (2.9)
	Not assessable	0	0	0
	Week 36, n (%)			
	n	10	5	15
	Normal	0	1 (20.0)	1 (6.7)
	Abnormal, not clinically significant	10 (100)	4 (80.0)	14 (93.3)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0
Echocardiogram	Baseline, n (%)			
	n	26	13	39
	Normal	14 (53.8)	10 (76.9)	24 (61.5)
	Abnormal, not clinically significant	11 (42.3)	3 (23.1)	14 (35.9)
	Abnormal, clinically significant	1 (3.8)[c]	0	1 (2.6)
	Not assessable	0	0	0
	Week 4, n (%)			
	n		13	36
	Normal	23	9 (69.2)	19 (52.8)
	Abnormal, not clinically significant	10 (43.5)	4 (30.8)	16 (44.4)
	Abnormal, clinically significant	12 (52.2)	0	0
	Not assessable	0	0	1 (2.8)
	Week 12, n (%)			
	n	24	12	36
	Normal	13 (54.2)	8 (66.7)	21 (58.3)
	Abnormal, not clinically significant	11 (45.8)	4 (33.3)	15 (41.7)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0

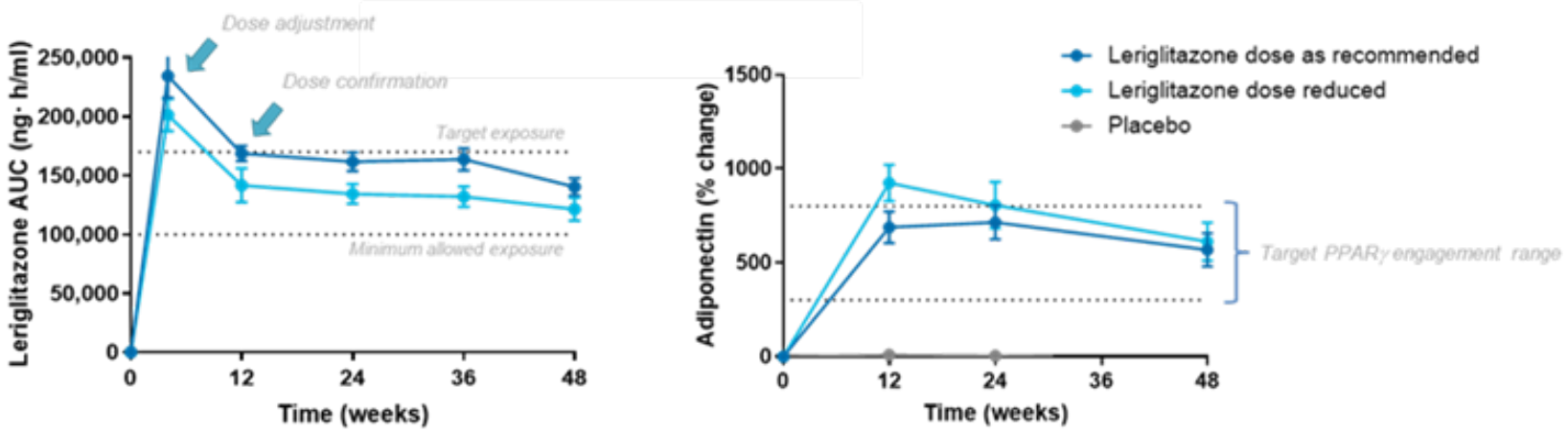
	Week 24, n (%)			
	n	22	12	34
	Normal	11 (50.0)	8 (66.7)	19 (55.9)
	Abnormal, not clinically significant	11 (50.0)	4 (33.3)	15 (44.1)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0
	Week 36, n (%)			
	n	10	5	15
	Normal	7 (70.0)	3 (60.0)	10 (66.7)
	Abnormal, not clinically significant	3 (30.0)	2 (40.0)	5 (33.3)
	Abnormal, clinically significant	0	0	0
	Not assessable	0	0	0
	Week 48, n (%)			
	n	20	12	32
	Normal	10 (50.0)	6 (50.0)	16 (50.0)
	Abnormal, not clinically significant	8 (40.0)	6 (50.0)	14 (43.8)
	Abnormal, clinically significant	2 (10.0)[d,e]	0	2 (6.3)
	Not assessable	0	0	0
	At follow-up, n (%)			
	n	25	12	37
	Normal	12 (48.0)	7 (58.3)	19 (51.4)
	Abnormal, not clinically significant	11 (44.0)	5 (41.7)	16 (43.2)
	Abnormal, clinically significant	2 (8.0)[f]	0	2 (5.4)
	Not assessable	0	0	0

[a]Reported as an AE of ‘T wave negativation V3 -V4’, no other relevant findings (similar findings were reported in subsequent visits as abnormal, not clinically significant); [b]Reported an AE of ‘T wave abnormal’ (Grade 1), assessed as not related to treatment. At the same visit, physical examination was normal and no clinically significant echocardiogram findings were

reported. [c]Rated as abnormal, not clinically significant at central reading. Medical history of hypertrophic cardiomyopathy. No relevant laboratory results, vital signs or physical examinations. [d]Hypotrophy recorded in a patient with a history of hypertrophic cardiomyopathy; no other clinically significant findings; rated as abnormal, not clinically significant at central reading. [f]Non-obstructive hypertrophic cardiomyopathy with conserved LVEF; no other clinically significant findings; rated as normal at central reading.

Interpretation of results was made by the site investigator. N values show the total number of patients in the safety analysis set; n values show the number of patients assessed at each timepoint. 12-lead ECG was collected post-dose for post-baseline assessments.

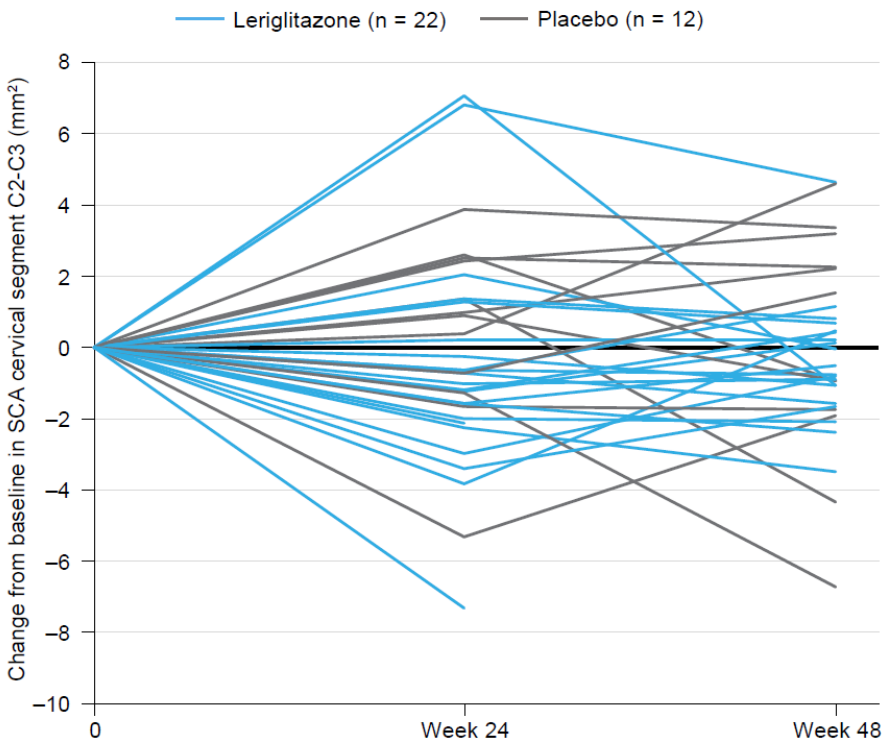
AE = adverse event; ECG = electrocardiogram.



eFigure 1 Pharmacokinetics and Adiponectin Results for the Leriglitazone and Placebo Groups Showing A) $AUC_{0\text{-}24}$ (ng·hr/mL) and B) Adiponectin (% change) From Baseline to Week 48

Data shown are mean ± SEM.

$AUC_{0\text{-}24}$ = area under the plasma concentration-time curve over the last 24-hr dosing interval at steady state; SEM = standard error of the mean.



	Mean (SD) SCA cervical segment C2-C3 (mm^2)		
	Baseline	Week 24	Week 48
Leriglitazone (n = 22 [20][a])	41.09 (4.95)	40.45 (4.83)	40.39 (5.28)
Placebo (n = 12)	40.20 (5.44)	40.71 (6.68)	40.26 (7.09)
Overall (n = 34 [32][a])	40.77 (5.062)	40.54 (5.45)	40.34 (5.91)
	Mean (SD) change from baseline in SCA cervical segment C2–C3 (mm^2)		
	Baseline	Week 24	Week 48
Leriglitazone (n = 20 [20][a])	-	−0.63 (3.14)	−0.38 (1.67)
Placebo (n = 12)	-	0.51 (2.48)	0.06 (3.40)
Overall (n = 34 [32][a])	-	−0.23 (2.94)	−0.22 (2.42)

[a]n for week 48

eFigure 2 Change From Baseline Over Time in Spinal Cord Area Cervical Segment C2-C3 (mm^2), Estimated From MRI T1-Weighted Brain Images (mITT Population).

The graph shows individual patient data at baseline, week 24, and week 48; the table shows the mean (SD) and mean change (SD) in SCA cervical segment C2-C3 area at baseline, week 24, and week 48. Baseline was defined as the last assessment done before or on study day 1.

mITT = modified intent-to-treat, SCA = spinal cord area; SD = standard deviation.

eTable 2 Results From the Secondary Efficacy Analyses (mITT Analysis Set)

Assessment			Leriglitazone (N = 22)	Placebo (N = 12)	*p* value
Biochemical magnetic resonance parameters	QSM for iron concentration	QSM, ppb			0.05
		Baseline, mean (SD)	64.89 (20.75)	73.86 (12.25)	
		Week 48, mean (SD)	63.67 (18.63)	71.14 (17.92)	
		Change from baseline to week 48[a]	n = 17	n = 9	
		LS mean (SE)	0.10 (1.33)	4.86 (1.84)	
		95% CI	−2.65, 2.85	1.05, 8.67	
	Cervical spinal cord tNAA/mIns ratio (assessed by MRS)	Ratio			0.25
		Baseline, mean (SD)	0.42 (0.10)	0.45 (0.10)	
		Week 48, mean (SD)	0.46 (0.10)	0.40 (0.09)	
		Change from baseline to week 48[a]	n = 16	n = 8	
		LS mean (SE)	0.03 (0.02)	−0.02 (0.03)	
		95% CI	−0.02, 0.08	[−0.08, 0.05	
Imaging	Dentate nuclei volume (normalized by TICV)	Baseline, mean (SD)	0.0025 (0.0005)	0.0024 (0.0006)	0.03
		Week 48, mean (SD)	0.0027 (0.0004)	0.0027 (0.0006)	
		Change from baseline to week 48[a]	n = 17	n = 9	
		LS mean (SE)	0.0002 (0.0001)	0.0005 (0.0001)	

Assessment			Leriglitazone (N = 22)	Placebo (N = 12)	*p* value
		95% CI	0.0001, 0.0003	0.0003, 0.0006	
Functional	CCFS[b]	Score			0.15
		Baseline, mean (SD)	1.13 (0.15)	1.10 (0.12)	
		Week 48, mean (SD)	1.13 (0.16)	1.12 (0.11)	
		Change from baseline to week 48[a]	n = 19	n = 12	
		LS mean (SE)	−0.01 (0.01)	0.01 (0.01)	
		95% CI	−0.02, 0.01	−0.01, 0.03	
Clinician-reported and patient-reported outcomes	SARA	Total score			0.76
		Baseline, mean (SD)	12.89 (4.87)	12.04 (4.32)	
		Week 48, mean (SD)	14.73 (7.17)	13.33 (3.77)	
		Change from baseline to week 48[a]	n = 20	n = 12	
		LS mean (SE)	1.72 (0.74)	1.35 (0.95)	
		95% CI	0.21; 3.23	−0.60;3.30	
	EQ-5D-5L	Sum of scores			0.79
		Baseline, mean (SD)	10.10 (3.69)	10.10 (3.68)	
		Week 48, mean (SD)	10.50 (3.02)	10.10 (3.63)	
		Change from baseline to week 48[a]	n = 20	n = 12	

Assessment			Leriglitazone (N = 22)	Placebo (N = 12)	*p* value
		LS mean (SE)	0.18 (0.52)	−0.05 (0.67)	
		95% CI	−0.88,1.24	−0.42,1.32	
Biochemical parameters in plasma	Gene expression frataxin	Ct			0.78
		Baseline, mean (SD)	28.90 (1.11)	28.99 (1.06)	
		Week 48, mean (SD)	28.98 (1.10)	28.97 (1.28)	
		Change from baseline to week 48[a]	n = 20	n =12	
		LS mean (SE)	0.05 (0.14)	−0.01 (0.18)	
		95% CI	−0.2, 0.3	−0.4, 0.3	

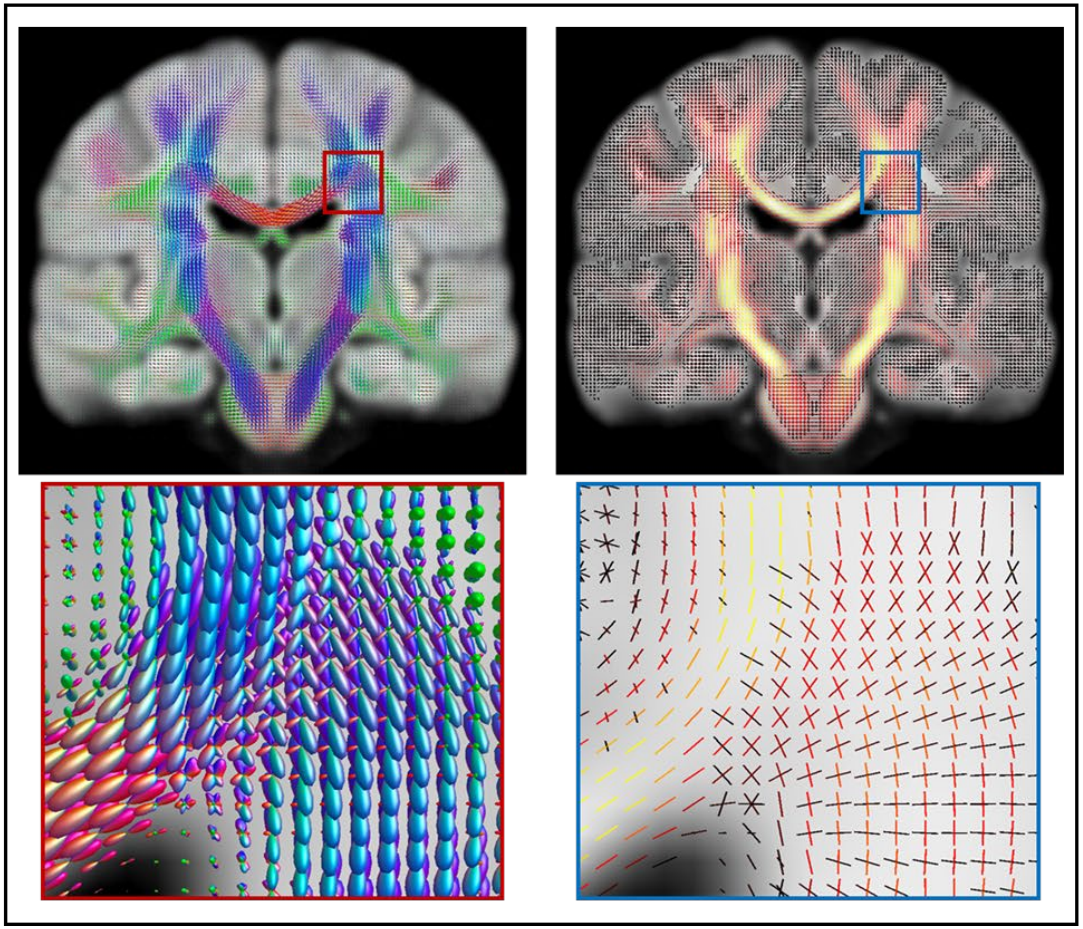
Abbreviations: ANCOVA = analysis of covariance; CCFS = cerebellar composite functional scale; CI = confidence interval; CST = corticospinal tract; EQ-5D-5L = 5-level, 5-dimension EuroQol questionnaire; FBA = fixel-based analysis; FC = fiber cross-section; FD = fiber density; FDC = fiber density and cross-section; LS = least-squares; mITT = modified intent-to-treat; MRS = magnetic resonance spectroscopy; QSM = quantitative susceptibility mapping; SARA = Scale for the Assessment and Rating of Ataxia; SD = standard deviation; SE = standard error; TICV = total intracranial volume; tNAA/mIns = total N-acetylaspartate concentration/myo-inositol.

N values show the total number of patients in the mITT analysis set; n values show the number of patients included in the ANCOVA analyses at week 48.

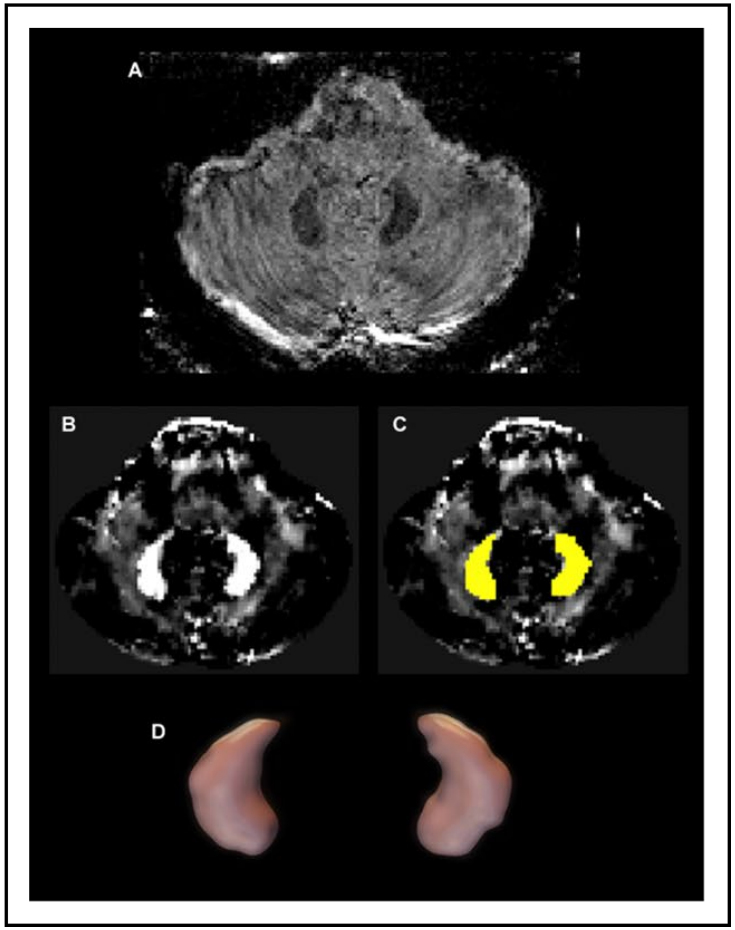
[a]Performed using an ANCOVA model with treatment arm as fixed effect and baseline value as covariate. The *p* value is for the difference between treatment arms.

[b]CCFS = $\log_{10}$ (7 + Z pegboard dominant hand / 10 + 4 * Z click dominant hand / 10).

1. Brain diffusion FBA



2. Dentate segmentation using QSM



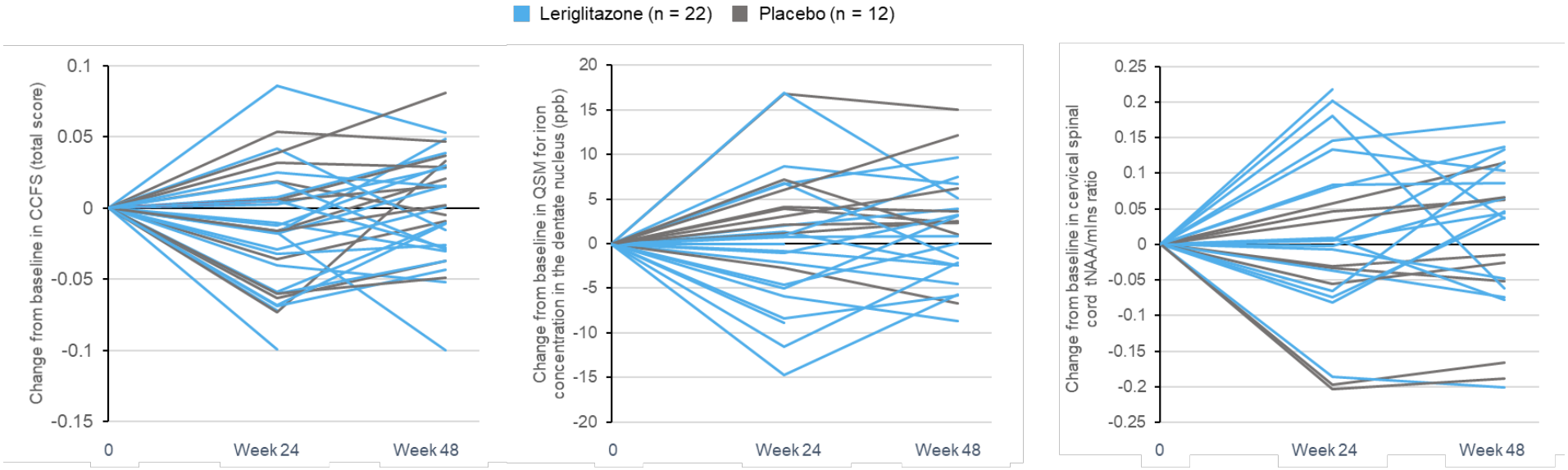
eFigure 3 Examples of MR Data.

1. Brain diffusion FBA images to evaluate individual fibers in a voxel. The upper panels show the fixel mask used to process the individual fibers in a voxel; the lower panels show the fiber orientation distribution from the constrained spherical deconvolution method.

2. Segmentation of the dentate from QSM images: image A shows the magnitude susceptibility-weighted images showing the bean-shaped dentate; image B shows the QSM images; image C shows an example of a manual region of interest drawn on a slice to initialize the automatic segmentation of the dentate with SUIT (manual segmentation was performed on four spaced-out slices for each side of the dentate); image D shows a 3D representation of the extracted dentate.

Examples of MR data for spinal cord morphometry, spinal cord DTI and spinal cord MRS (acquired with very similar parameters as those used in the FRAMES study), can be found in: Joers JM, Adanyeguh, IM, Deelchand, DK *et al*. Spinal cord MRI and MRS detect early-stage alterations and disease progression in Friedreich Ataxia. medRxiv: 2022:2022.01.28.22270048 [Preprint; 33 pp.]. 2022. Available from: https://doi.org/10.1101/2022.01.28.22270048 (Accessed 01 April 2022).

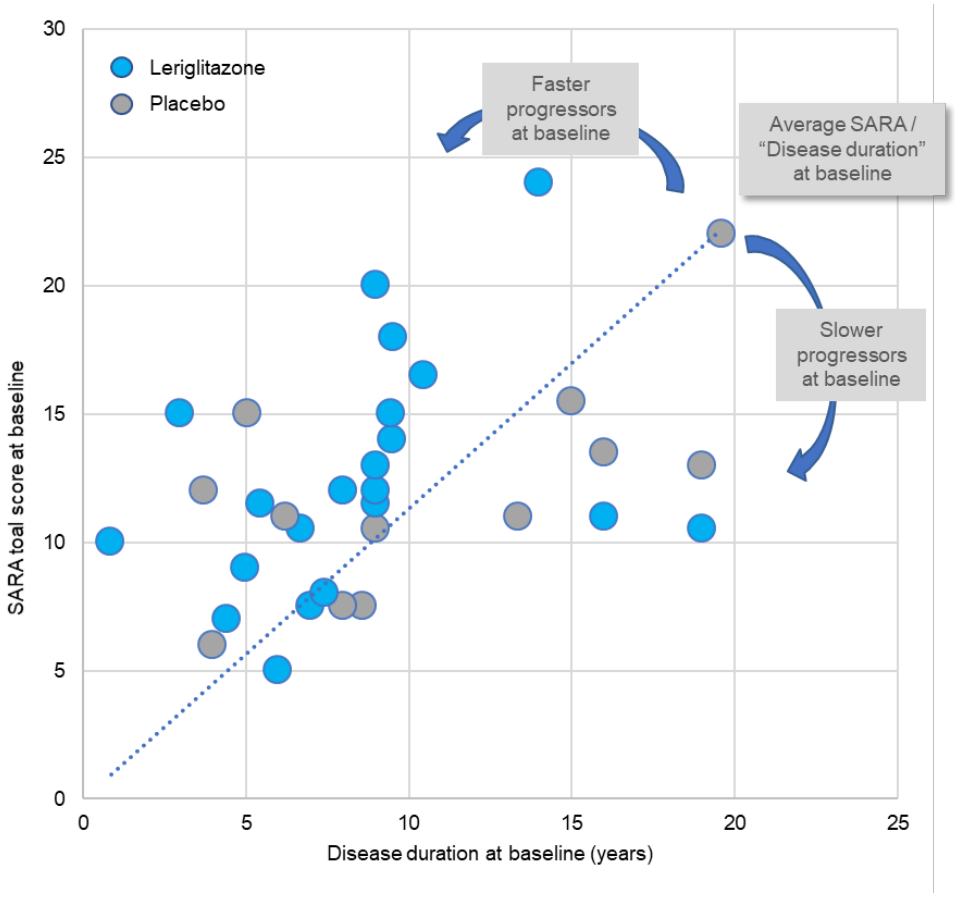
FBA = fixel-base analysis; MR = magnetic resonance; QSM = quantitative susceptibility mapping; SUIT = spatially unbiased atlas template of the cerebellum and brainstem toolbox.



eFigure 4 Change From Baseline Over Time in A) CCFS (Total Score), B) QSM for Iron Concentration in the Dentate Nucleus (ppb) and C) cervical spinal cord tNAA/mIns ratio by MRS (mITT population)

Data show individual patient data at baseline, week 24, and week 48. Baseline was defined as the last assessment done before or on study day 1.

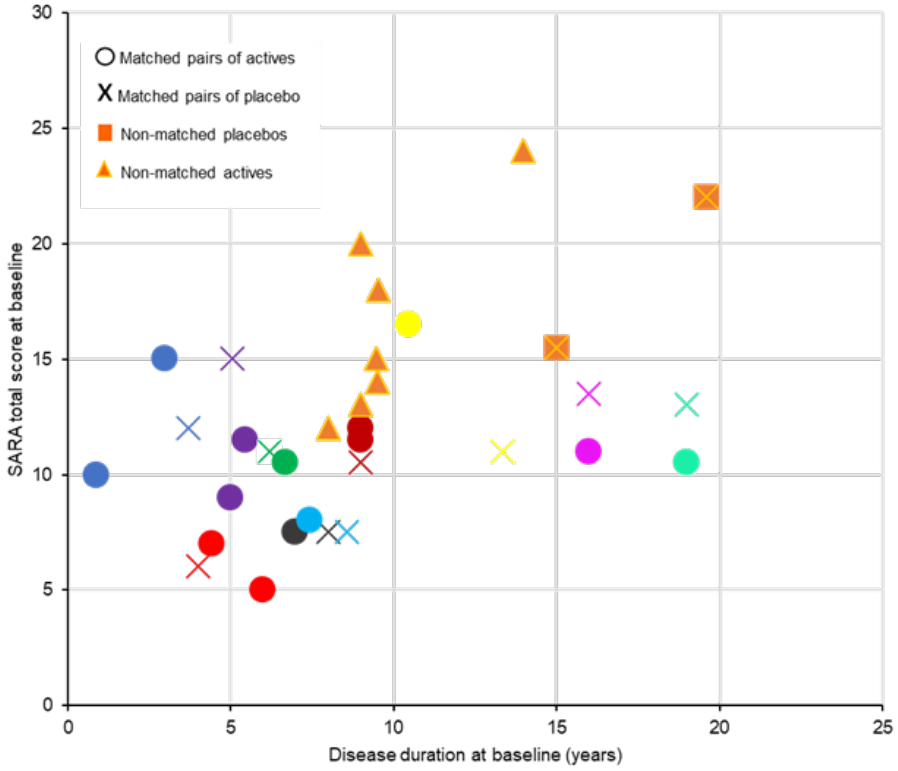
CCFS = cerebellar composite functional scale; mITT = modified intent-to-treat; MRS = magnetic resonance spectroscopy; QSM = quantitative susceptibility mapping; tNAA/mIns = total *N*-acetylaspartate concentration/myo-inositol.



eFigure 5 Disease Progression as Measured by Disease Duration and SARA Total Score at Baseline (mITT Population; Sub-Population Analysis)

The regression line is the result of data from all patients, assumes a SARA total score of 0 when disease duration is 0, and an average increase of 1.13 SARA points per year.

mITT = modified intent-to-treat; SARA = Scale for the Assessment and Rating of Ataxia.



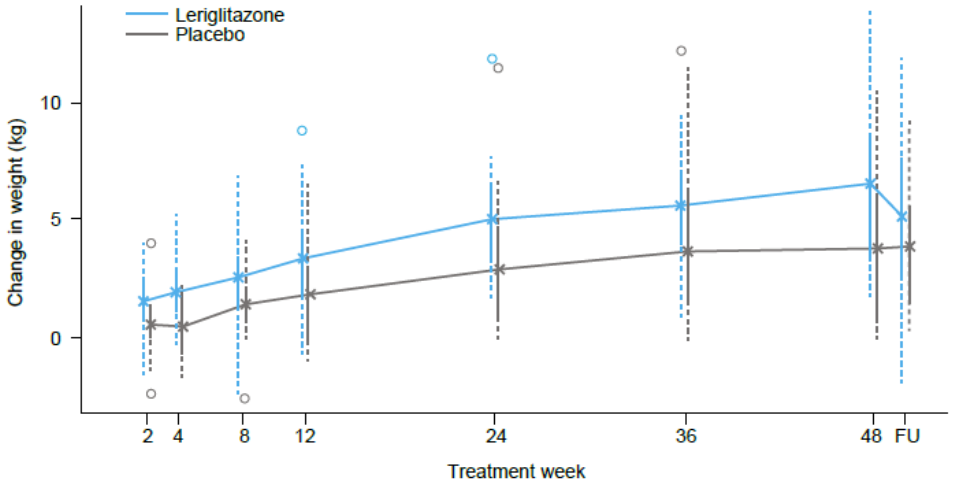
Secondary endpoint	Week 48				*p* value
	Leriglitazone		Placebo		
	n	LS mean change (95% CI)	n	LS mean change (95% CI)	
SARA total score	13	0.72 (−1.20, 2.64)	10	1.96 (0.09, 3.84)	0.26
ADL total score	13	−0.46 (-2.10, 1.18)	10	0.88 (−0.74, 2.49)	0.08
CCFS total score	12	0.00 (−0.02, 0.02)	10	0.02 (−0.00, 0.04)	0.06
QSM signal dentate nucleus	10	−0.86 (−3.86, 2.14)	7	4.05 (0.99, 7.12)	0.01
tNAA/mIns ratio	11	0.025 (−0.03, 0.08)	6	0.00 (−0.06, 0.06)	0.47

eFigure 6. Matching Patient Pairs Across Treatment Groups (mITT Population; Sub-population Analysis)

The graph shows manually matched patients based on disease duration and SARA at baseline. In total, 24 out of 34 patients were matched. The table shows the LS mean change (95% CI) from baseline at week 48 and *p* values for the difference between treatment arms, as assessed by ANCOVA (with treatment arm as a fixed effect and the baseline as a

covariate). Baseline was defined as the last assessment done before or on study day 1. The n values in the table show the number of patients included in each ANCOVA analysis.

ADL = activities of daily living; ANCOVA = analysis of covariance; CCFS = composite cerebellar functional severity; LS = least-squares; mITT = modified intent-to-treat; QSM = quantitative susceptibility mapping; SARA = Scale for the Assessment and Rating of Ataxia; tNAA/mIns = total *N*-acetylaspartate concentration/myo-inositol.



	2	4	8	12	24	36	48	FU
Leriglitazone (n)	23	26	25	25	22	20	20	24
Placebo (n)	13	13	12	12	12	12	12	12

eFigure 7. Vital Signs: Change From Baseline in Body Weight Over Time (Safety Population)

The box corresponds to the IQR of which the upper bound is the 75th percentile, the lower bound is the 25th percentile and the horizontal line within the box is the median. The upper whisker corresponds to the minimum value between max and 75th percentile + 1.5 × IQR and the lower whisker corresponds to the maximum value between min and 25th percentile −1.5 × IQR. Extreme values are displayed outside whiskers. The mean is identified by the x symbol. The method used is inclusive. The n values in the table show the number of patients assessed at each week.

FU = follow-up; IQR = interquartile range.

eTable 3. Individual Patient Data for Septal Wall Thickness in Diastole (mm) and Left Ventricular Mass (g/m^2) Over Time (Cohort of Safety Population)

				STANDARD RANGE		
PATIENT NUMBER	**TEST**	**RESULT**	**UNITS**	**Low**	**High**	**VISIT**
1	Septal Wall Thickness in	11.0	mm	6	10	Visit 2 - V2
1	Diastole LV Mass	88.76	g/m2	50	102	Visit 2 - V2
1	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 3 - V3
1	LV Mass	103.9	g/m2	50	102	Visit 3 - V3
1	Septal Wall Thickness in Diastole	12.0	mm	6	10	Visit 4 - V4
1	LV Mass	76.36	g/m2	50	102	Visit 4 - V4
1	Septal Wall Thickness in Diastole	13.0	mm	6	10	End of Treatment Visit
1	LV Mass	71.55	g/m2	50	102	End of Treatment Visit
1	Septal Wall Thickness in Diastole	10.0	mm	6	10	Follow up Visit
1	LV Mass	78.24	g/m2	50	102	Follow up Visit
1	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
1	LV Mass			50	102	Visit 1 - V1
2	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
2	LV Mass	0.0	g/m2	44	88	Visit 2 - V2
2	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 3 - V3
2	LV Mass	105.8	g/m2	44	88	Visit 3 - V3
2	Septal Wall Thickness in Diastole	12.0	mm	6	10	End of Treatment Visit
2	LV Mass	115.8	g/m2	44	88	End of Treatment Visit
2	Septal Wall Thickness in Diastole	10.0	mm	6	10	Follow up Visit
2	LV Mass	78.54	g/m2	44	88	Follow up Visit
2	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
2	LV Mass			44	88	Visit 1 - V1
3	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 2 - V2
3	LV Mass	100.8	g/m2	44	88	Visit 2 - V2
3	Septal Wall Thickness in Diastole	10.0	mm	6	10	End of Treatment Visit
3	LV Mass	91.6	g/m2	44	88	End of Treatment Visit
3	Septal Wall Thickness in Diastole	11.0	mm	6	10	Follow up Visit
3	LV Mass	99.7	g/m2	44	88	Follow up Visit
3	Septal Wall Thickness in Diastole	10.2	mm	6	10	Visit 1 - V1
3	LV Mass	149.19	g/m2	44	88	Visit 1 - V1
3	Septal Wall Thickness in Diastole	12.0	mm	6	10	Unscheduled Visit
3	LV Mass	102.6	g/m2	44	88	Unscheduled Visit
4	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
4	LV Mass	0.0	g/m2	50	102	Visit 2 - V2
4	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
4	LV Mass			50	102	Visit 3 - V3
4	Septal Wall Thickness in Diastole	12.0	mm	6	10	End of Treatment Visit
4	LV Mass	103.38	g/m2	50	102	End of Treatment Visit
4	Septal Wall Thickness in Diastole	12.0	mm	6	10	Follow up Visit
4	LV Mass	112.02	g/m2	50	102	Follow up Visit
4	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
4	LV Mass	0.0	g/m2	50	102	Visit 1 - V1
5	Septal Wall Thickness in Diastole	7.0	mm	6	10	Visit 2 - V2
5	LV Mass	69.4	g/m2	50	102	Visit 2 - V2
5	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 3 - V3
5	LV Mass	73.9	g/m2	50	102	Visit 3 - V3
5	Septal Wall Thickness in Diastole	5.0	mm	6	10	Visit 4 - V4
5	LV Mass	56.2	g/m2	50	102	Visit 4 - V4
5	Septal Wall Thickness in Diastole	6.0	mm	6	10	End of Treatment Visit
5	LV Mass	65.48	g/m2	50	102	End of Treatment Visit
5	Septal Wall Thickness in Diastole	9.0	mm	6	10	Follow up Visit
5	LV Mass	73.79	g/m2	50	102	Follow up Visit
5	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
5	LV Mass			50	102	Visit 1 - V1
5	Septal Wall Thickness in Diastole	9.0	mm	6	10	Unscheduled Visit
5	LV Mass	86.7	g/m2	50	102	Unscheduled Visit
6	Septal Wall Thickness in Diastole			6	10	Follow up Visit
6	LV Mass			50	102	Follow up Visit
6	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
6	LV Mass			50	102	Visit 1 - V1
7	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
7	LV Mass			50	102	Visit 2 - V2
7	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 3 - V3
7	LV Mass	66.55	g/m2	50	102	Visit 3 - V3
7	Septal Wall Thickness in Diastole	7.0	mm	6	10	End of Treatment Visit
7	LV Mass	57.26	g/m2	50	102	End of Treatment Visit
7	Septal Wall Thickness in Diastole	10.0	mm	6	10	Follow up Visit
7	LV Mass	97.32	g/m2	50	102	Follow up Visit
7	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
7	LV Mass			50	102	Visit 1 - V1
7	Septal Wall Thickness in Diastole	10.0	mm	6	10	Unscheduled Visit
7	LV Mass	76.53	g/m2	50	102	Unscheduled Visit
7	Septal Wall Thickness in Diastole	12.0	mm	6	10	Unscheduled Visit
7	LV Mass	122.0	g/m2	50	102	Unscheduled Visit

8	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 2 - V2
8	LV Mass	91.3	g/m2	50	102	Visit 2 - V2
8	Septal Wall Thickness in Diastole	10.5	mm	6	10	Visit 3 - V3
8	LV Mass	64.31	g/m2	50	102	Visit 3 - V3
8	Septal Wall Thickness in Diastole	10.7	mm	6	10	End of Treatment Visit
8	LV Mass	76.49	g/m2	50	102	End of Treatment Visit
8	Septal Wall Thickness in Diastole	8.6	mm	6	10	Follow up Visit
8	LV Mass	59.33	g/m2	50	102	Follow up Visit
8	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
8	LV Mass			50	102	Visit 1 - V1
9	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
9	LV Mass			50	102	Visit 2 - V2
9	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 3 - V3
9	LV Mass	73.65	g/m2	50	102	Visit 3 - V3
9	Septal Wall Thickness in Diastole	10.0	mm	6	10	End of Treatment Visit
9	LV Mass	86.48	g/m2	50	102	End of Treatment Visit
9	Septal Wall Thickness in Diastole	8.0	mm	6	10	Follow up Visit
9	LV Mass	54.03	g/m2	50	102	Follow up Visit
9	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
9	LV Mass			50	102	Visit 1 - V1
10	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
10	LV Mass			44	88	Visit 2 - V2
10	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
10	LV Mass			44	88	Visit 3 - V3
10	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 4 - V4
10	LV Mass	69.77	g/m2	44	88	Visit 4 - V4
10	Septal Wall Thickness in Diastole	10.0	mm	6	10	End of Treatment Visit
10	LV Mass	92.14	g/m2	44	88	End of Treatment Visit
10	Septal Wall Thickness in Diastole			6	10	Follow up Visit
10	LV Mass			44	88	Follow up Visit
10	Septal Wall Thickness in Diastole	9.0	mm	6	10	Unscheduled Visit
10	LV Mass			44	88	Unscheduled Visit
11	Septal Wall Thickness in Diastole	11.0	mm	N/A	N/A	Visit 2 - V2
11	LV Mass	91.0	g/m2	N/A	N/A	Visit 2 - V2
11	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Visit 3 - V3
11	LV Mass	98.0	g/m2	N/A	N/A	Visit 3 - V3
11	Septal Wall Thickness in Diastole	12.8	mm	N/A	N/A	Visit 4 - V4
11	LV Mass	107.87	g/m2	N/A	N/A	Visit 4 - V4
11	Septal Wall Thickness in Diastole	12.0	mm	N/A	N/A	End of Treatment Visit
11	LV Mass	91.42	g/m2	N/A	N/A	End of Treatment Visit
11	Septal Wall Thickness in Diastole	12.0	mm	N/A	N/A	Follow up Visit
11	LV Mass	91.82	g/m2	N/A	N/A	Follow up Visit
11	Septal Wall Thickness in Diastole	15.0	mm	N/A	N/A	Unscheduled Visit
11	LV Mass	88.7	g/m2	N/A	N/A	Unscheduled Visit
12	Septal Wall Thickness in Diastole	13.0	mm	N/A	N/A	Visit 2 - V2
12	LV Mass	91.3	g/m2	N/A	N/A	Visit 2 - V2
12	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	Visit 3 - V3
12	LV Mass	62.8	g/m2	N/A	N/A	Visit 3 - V3
12	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	End of Treatment Visit
12	LV Mass	81.12	g/m2	N/A	N/A	End of Treatment Visit
12	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Follow up Visit
12	LV Mass	81.86	g/m2	N/A	N/A	Follow up Visit
12	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 1 - V1
12	LV Mass	78.1	g/m2	N/A	N/A	Visit 1 - V1
13	Septal Wall Thickness in Diastole			N/A	N/A	Visit 2 - V2
13	LV Mass			N/A	N/A	Visit 2 - V2
13	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Visit 3 - V3
13	LV Mass	45.27	g/m2	N/A	N/A	Visit 3 - V3
13	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	End of Treatment Visit
13	LV Mass	48.71	g/m2	N/A	N/A	End of Treatment Visit
13	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Follow up Visit
13	LV Mass	67.64	g/m2	N/A	N/A	Follow up Visit
13	Septal Wall Thickness in Diastole			N/A	N/A	Visit 1 - V1
13	LV Mass			N/A	N/A	Visit 1 - V1
14	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 2 - V2
14	LV Mass	50.0	g/m2	50	102	Visit 2 - V2
14	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
14	LV Mass			50	102	Visit 3 - V3
14	Septal Wall Thickness in Diastole	9.0	mm	6	10	End of Treatment Visit
14	LV Mass	70.01	g/m2	50	102	End of Treatment Visit
14	Septal Wall Thickness in Diastole	9.7	mm	6	10	Follow up Visit
14	LV Mass	56.67	g/m2	50	102	Follow up Visit
14	Septal Wall Thickness in Diastole	6.0	mm	6	10	Visit 1 - V1
14	LV Mass	45.26	g/m2	50	102	Visit 1 - V1

15	Septal Wall Thickness in Diastole	8.7	mm	6	10	Visit 3 - V3
15	LV Mass	75.81	g/m2	44	88	Visit 3 - V3
15	Septal Wall Thickness in Diastole	9.0	mm	6	10	Follow up Visit
15	LV Mass	88.23	g/m2	44	88	Follow up Visit
15	Septal Wall Thickness in Diastole	11.0	mm	6	10	Unscheduled Visit
15	LV Mass	100.1	g/m2	44	88	Unscheduled Visit
15	Septal Wall Thickness in Diastole	8.0	mm	6	10	Unscheduled Visit
15	LV Mass	72.4	g/m2	44	88	Unscheduled Visit
15	Septal Wall Thickness in Diastole	9.0	mm	6	10	Unscheduled Visit
15	LV Mass	87.0	g/m2	44	88	Unscheduled Visit
16	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 2 - V2
16	LV Mass	70.6	g/m2	N/A	N/A	Visit 2 - V2
16	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Visit 3 - V3
16	LV Mass	85.92	g/m2	N/A	N/A	Visit 3 - V3
16	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	Visit 4 - V4
16	LV Mass	82.59	g/m2	N/A	N/A	Visit 4 - V4
16	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	End of Treatment Visit
16	LV Mass	52.17	g/m2	N/A	N/A	End of Treatment Visit
16	Septal Wall Thickness in Diastole	7.8	mm	N/A	N/A	Follow up Visit
16	LV Mass	73.01	g/m2	N/A	N/A	Follow up Visit
16	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 1 - V1
16	LV Mass	76.1	g/m2	N/A	N/A	Visit 1 - V1
17	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 2 - V2
17	LV Mass	74.7	g/m2	44	88	Visit 2 - V2
17	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
17	LV Mass			44	88	Visit 3 - V3
17	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 4 - V4
17	LV Mass	83.59	g/m2	44	88	Visit 4 - V4
17	Septal Wall Thickness in Diastole	7.0	mm	6	10	End of Treatment Visit
17	LV Mass	64.44	g/m2	44	88	End of Treatment Visit
17	Septal Wall Thickness in Diastole	8.0	mm	6	10	Follow up Visit
17	LV Mass	56.02	g/m2	44	88	Follow up Visit
17	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
17	LV Mass			44	88	Visit 1 - V1
18	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
18	LV Mass			44	88	Visit 2 - V2
18	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
18	LV Mass			44	88	Visit 3 - V3
18	Septal Wall Thickness in Diastole	6.0	mm	6	10	Visit 4 - V4
18	LV Mass	76.0	g/m2	44	88	Visit 4 - V4
18	Septal Wall Thickness in Diastole			6	10	End of Treatment Visit
18	LV Mass			44	88	End of Treatment Visit
18	Septal Wall Thickness in Diastole			6	10	Follow up Visit
18	LV Mass			44	88	Follow up Visit
18	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
18	LV Mass			44	88	Visit 1 - V1
18	Septal Wall Thickness in Diastole	6.0	mm	6	10	Unscheduled Visit
18	LV Mass	61.0	g/m2	44	88	Unscheduled Visit
19	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 2 - V2
19	LV Mass	84.66	g/m2	50	102	Visit 2 - V2
19	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 3 - V3
19	LV Mass	67.8	g/m2	50	102	Visit 3 - V3
19	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 4 - V4
19	LV Mass	63.28	g/m2	50	102	Visit 4 - V4
19	Septal Wall Thickness in Diastole	11.0	mm	6	10	End of Treatment Visit
19	LV Mass	82.72	g/m2	50	102	End of Treatment Visit
19	Septal Wall Thickness in Diastole	9.8	mm	6	10	Follow up Visit
19	LV Mass	70.59	g/m2	50	102	Follow up Visit
19	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
19	LV Mass			50	102	Visit 1 - V1
20	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Visit 2 - V2
20	LV Mass	80.4	g/m2	N/A	N/A	Visit 2 - V2
20	Septal Wall Thickness in Diastole	6.0	mm	N/A	N/A	Visit 3 - V3
20	LV Mass	69.9	g/m2	N/A	N/A	Visit 3 - V3
20	Septal Wall Thickness in Diastole	5.0	mm	N/A	N/A	End of Treatment Visit
20	LV Mass	52.17	g/m2	N/A	N/A	End of Treatment Visit
20	Septal Wall Thickness in Diastole	5.1	mm	N/A	N/A	Follow up Visit
20	LV Mass	48.86	g/m2	N/A	N/A	Follow up Visit
20	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 1 - V1
20	LV Mass	93.07	g/m2	N/A	N/A	Visit 1 - V1

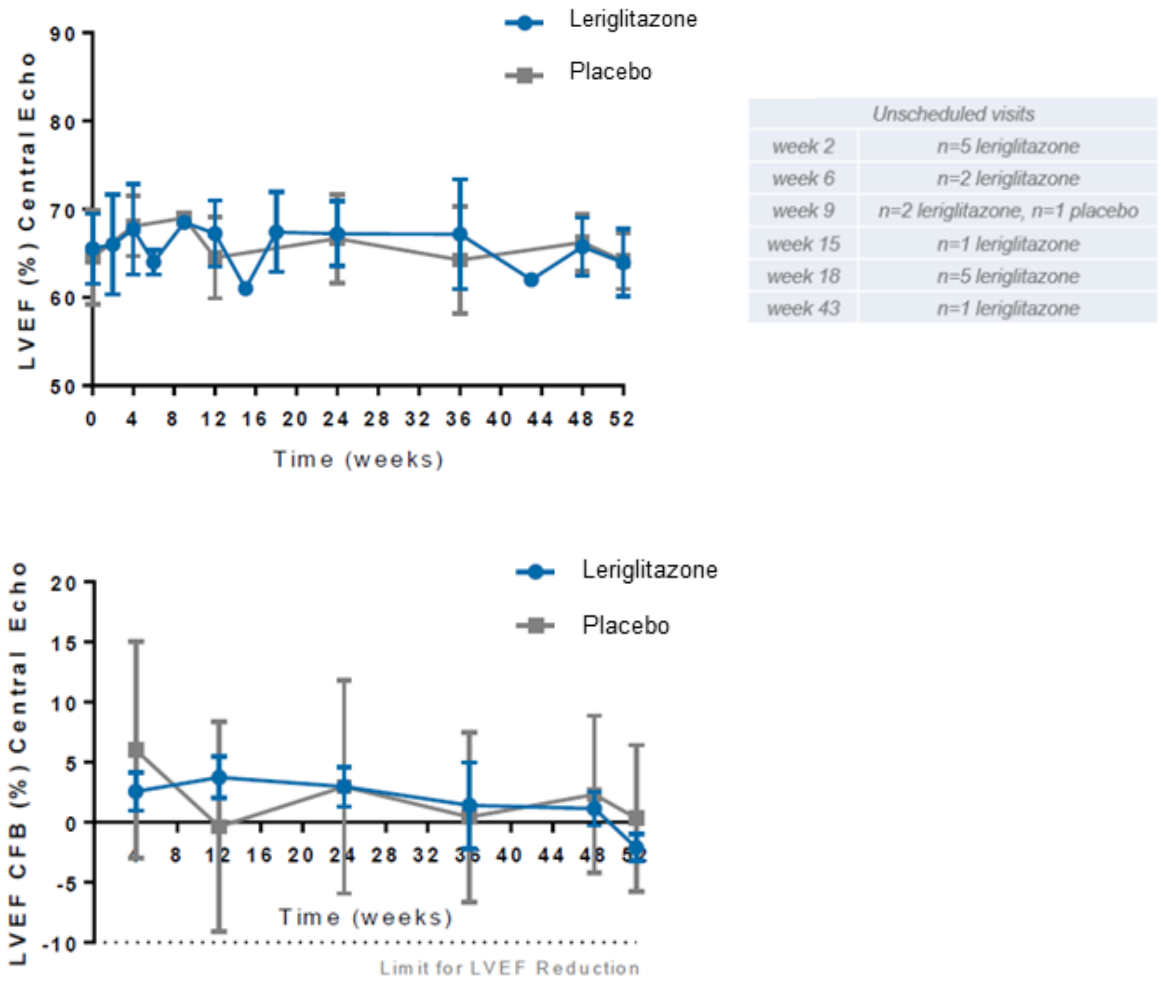
21	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 2 - V2
21	LV Mass	95.6	g/m2	44	88	Visit 2 - V2
21	Septal Wall Thickness in Diastole	12.0	mm	6	10	Visit 3 - V3
21	LV Mass	97.6	g/m2	44	88	Visit 3 - V3
21	Septal Wall Thickness in Diastole	12.0	mm	6	10	End of Treatment Visit
21	LV Mass	100.51	g/m2	44	88	End of Treatment Visit
21	Septal Wall Thickness in Diastole	13.0	mm	6	10	Follow up Visit
21	LV Mass	97.79	g/m2	44	88	Follow up Visit
21	Septal Wall Thickness in Diastole	14.0	mm	6	10	Visit 1 - V1
21	LV Mass	109.8	g/m2	44	88	Visit 1 - V1
21	Septal Wall Thickness in Diastole			6	10	Unscheduled Visit
21	LV Mass			44	88	Unscheduled Visit
21	Septal Wall Thickness in Diastole	15.0	mm	6	10	Unscheduled Visit
21	LV Mass	110.4	g/m2	44	88	Unscheduled Visit
22	Septal Wall Thickness in Diastole	12.0	mm	N/A	N/A	Visit 2 - V2
22	LV Mass	125.5	g/m2	N/A	N/A	Visit 2 - V2
22	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	Visit 3 - V3
22	LV Mass	185.5	g/m2	N/A	N/A	Visit 3 - V3
22	Septal Wall Thickness in Diastole	12.7	mm	N/A	N/A	End of Treatment Visit
22	LV Mass	139.59	g/m2	N/A	N/A	End of Treatment Visit
22	Septal Wall Thickness in Diastole	13.1	mm	N/A	N/A	Follow up Visit
22	LV Mass	125.63	g/m2	N/A	N/A	Follow up Visit
22	Septal Wall Thickness in Diastole			N/A	N/A	Visit 1 - V1
22	LV Mass			N/A	N/A	Visit 1 - V1
23	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 2 - V2
23	LV Mass	71.7	g/m2	N/A	N/A	Visit 2 - V2
23	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	Visit 3 - V3
23	LV Mass	44.7	g/m2	N/A	N/A	Visit 3 - V3
23	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	End of Treatment Visit
23	LV Mass	61.18	g/m2	N/A	N/A	End of Treatment Visit
23	Septal Wall Thickness in Diastole	10.3	mm	N/A	N/A	Follow up Visit
23	LV Mass	86.28	g/m2	N/A	N/A	Follow up Visit
23	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 1 - V1
23	LV Mass	77.0	g/m2	N/A	N/A	Visit 1 - V1
24	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 2 - V2
24	LV Mass	44.7	g/m2	44	88	Visit 2 - V2
24	Septal Wall Thickness in Diastole	7.0	mm	6	10	Visit 3 - V3
24	LV Mass	45.26	g/m2	44	88	Visit 3 - V3
24	Septal Wall Thickness in Diastole	7.0	mm	6	10	End of Treatment Visit
24	LV Mass	37.62	g/m2	44	88	End of Treatment Visit
24	Septal Wall Thickness in Diastole			6	10	Follow up Visit
24	LV Mass			44	88	Follow up Visit
24	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
24	LV Mass			44	88	Visit 1 - V1
25	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	Visit 2 - V2
25	LV Mass	65.2	g/m2	N/A	N/A	Visit 2 - V2
25	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	Visit 3 - V3
25	LV Mass	70.83	g/m2	N/A	N/A	Visit 3 - V3
25	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Visit 4 - V4
25	LV Mass	70.93	g/m2	N/A	N/A	Visit 4 - V4
25	Septal Wall Thickness in Diastole	9.0	mm	N/A	N/A	End of Treatment Visit
25	LV Mass	76.94	g/m2	N/A	N/A	End of Treatment Visit
25	Septal Wall Thickness in Diastole			N/A	N/A	Follow up Visit
25	LV Mass			N/A	N/A	Follow up Visit
25	Septal Wall Thickness in Diastole			N/A	N/A	Visit 1 - V1
25	LV Mass			N/A	N/A	Visit 1 - V1
26	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 2 - V2
26	LV Mass	103.47	g/m2	50	102	Visit 2 - V2
26	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
26	LV Mass			50	102	Visit 1 - V1
27	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
27	LV Mass	0.0	g/m2	50	102	Visit 2 - V2
27	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
27	LV Mass			50	102	Visit 3 - V3
27	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 4 - V4
27	LV Mass	58.09	g/m2	50	102	Visit 4 - V4
27	Septal Wall Thickness in Diastole	7.0	mm	6	10	End of Treatment Visit
27	LV Mass	93.62	g/m2	50	102	End of Treatment Visit
27	Septal Wall Thickness in Diastole			6	10	Follow up Visit
27	LV Mass			50	102	Follow up Visit
27	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 1 - V1
27	LV Mass	99.3	g/m2	50	102	Visit 1 - V1

28	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 2 - V2
28	LV Mass	56.0	g/m2	50	102	Visit 2 - V2
28	Septal Wall Thickness in Diastole	6.0	mm	6	10	Visit 3 - V3
28	LV Mass	46.4	g/m2	50	102	Visit 3 - V3
28	Septal Wall Thickness in Diastole	7.0	mm	6	10	Visit 4 - V4
28	LV Mass	48.67	g/m2	50	102	Visit 4 - V4
28	Septal Wall Thickness in Diastole	8.0	mm	6	10	End of Treatment Visit
28	LV Mass	55.58	g/m2	50	102	End of Treatment Visit
28	Septal Wall Thickness in Diastole	7.2	mm	6	10	Follow up Visit
28	LV Mass	51.98	g/m2	50	102	Follow up Visit
28	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
28	LV Mass			50	102	Visit 1 - V1
28	Septal Wall Thickness in Diastole	7.0	mm	6	10	Unscheduled Visit
28	LV Mass	49.85	g/m2	50	102	Unscheduled Visit
29	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
29	LV Mass			44	88	Visit 1 - V1
30	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
30	LV Mass			50	102	Visit 2 - V2
30	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 3 - V3
30	LV Mass	73.5	g/m2	50	102	Visit 3 - V3
30	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 4 - V4
30	LV Mass	70.08	g/m2	50	102	Visit 4 - V4
30	Septal Wall Thickness in Diastole	9.3	mm	6	10	End of Treatment Visit
30	LV Mass	51.44	g/m2	50	102	End of Treatment Visit
30	Septal Wall Thickness in Diastole	10.0	mm	6	10	Follow up Visit
30	LV Mass	68.71	g/m2	50	102	Follow up Visit
30	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
30	LV Mass			50	102	Visit 1 - V1
31	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
31	LV Mass			50	102	Visit 2 - V2
31	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 3 - V3
31	LV Mass	78.25	g/m2	50	102	Visit 3 - V3
31	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 4 - V4
31	LV Mass	83.52	g/m2	50	102	Visit 4 - V4
31	Septal Wall Thickness in Diastole	11.0	mm	6	10	End of Treatment Visit
31	LV Mass	88.73	g/m2	50	102	End of Treatment Visit
31	Septal Wall Thickness in Diastole	10.2	mm	6	10	Follow up Visit
31	LV Mass	77.23	g/m2	50	102	Follow up Visit
31	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
31	LV Mass			50	102	Visit 1 - V1
32	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 2 - V2
32	LV Mass	90.0	g/m2	50	102	Visit 2 - V2
32	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 3 - V3
32	LV Mass	119.33	g/m2	50	102	Visit 3 - V3
32	Septal Wall Thickness in Diastole	12.0	mm	6	10	Visit 4 - V4
32	LV Mass	105.07	g/m2	50	102	Visit 4 - V4
32	Septal Wall Thickness in Diastole	11.0	mm	6	10	End of Treatment Visit
32	LV Mass	122.89	g/m2	50	102	End of Treatment Visit
32	Septal Wall Thickness in Diastole	10.5	mm	6	10	Follow up Visit
32	LV Mass	100.66	g/m2	50	102	Follow up Visit
32	Septal Wall Thickness in Diastole	8.0	mm	6	10	Visit 1 - V1
32	LV Mass	86.0	g/m2	50	102	Visit 1 - V1
33	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	Visit 2 - V2
33	LV Mass	59.7	g/m2	N/A	N/A	Visit 2 - V2
33	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Follow up Visit
33	LV Mass	65.3	g/m2	N/A	N/A	Follow up Visit
33	Septal Wall Thickness in Diastole	6.0	mm	N/A	N/A	Visit 1 - V1
33	LV Mass	53.4	g/m2	N/A	N/A	Visit 1 - V1
33	Septal Wall Thickness in Diastole	7.0	mm	N/A	N/A	Unscheduled Visit
33	LV Mass	61.5	g/m2	N/A	N/A	Unscheduled Visit
33	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	Unscheduled Visit
33	LV Mass	64.0	g/m2	N/A	N/A	Unscheduled Visit
33	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	Unscheduled Visit
33	LV Mass	64.6	g/m2	N/A	N/A	Unscheduled Visit
34	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 2 - V2
34	LV Mass	71.2	g/m2	50	102	Visit 2 - V2
34	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
34	LV Mass			50	102	Visit 3 - V3
34	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 4 - V4
34	LV Mass	87.52	g/m2	50	102	Visit 4 - V4
34	Septal Wall Thickness in Diastole	10.0	mm	6	10	End of Treatment Visit
34	LV Mass	80.25	g/m2	50	102	End of Treatment Visit
34	Septal Wall Thickness in Diastole	8.6	mm	6	10	Follow up Visit
34	LV Mass	75.59	g/m2	50	102	Follow up Visit
34	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 1 - V1
34	LV Mass	53.6	g/m2	50	102	Visit 1 - V1
34	Septal Wall Thickness in Diastole	9.0	mm	6	10	Unscheduled Visit
34	LV Mass	49.3	g/m2	50	102	Unscheduled Visit

35	Septal Wall Thickness in Diastole			6	10	Visit 2 - V2
35	LV Mass			50	102	Visit 2 - V2
35	Septal Wall Thickness in Diastole			6	10	Visit 3 - V3
35	LV Mass			50	102	Visit 3 - V3
35	Septal Wall Thickness in Diastole			6	10	End of Treatment Visit
35	LV Mass			50	102	End of Treatment Visit
35	Septal Wall Thickness in Diastole			6	10	Follow up Visit
35	LV Mass			50	102	Follow up Visit
35	Septal Wall Thickness in Diastole			6	10	Visit 1 - V1
35	LV Mass			50	102	Visit 1 - V1
36	Septal Wall Thickness in Diastole	10.0	mm	6	10	Visit 2 - V2
36	LV Mass	97.8	g/m2	44	88	Visit 2 - V2
36	Septal Wall Thickness in Diastole	11.0	mm	6	10	Visit 3 - V3
36	LV Mass	89.5	g/m2	44	88	Visit 3 - V3
36	Septal Wall Thickness in Diastole	9.0	mm	6	10	End of Treatment Visit
36	LV Mass	87.61	g/m2	44	88	End of Treatment Visit
36	Septal Wall Thickness in Diastole	10.2	mm	6	10	Follow up Visit
36	LV Mass	81.16	g/m2	44	88	Follow up Visit
36	Septal Wall Thickness in Diastole	7.0	mm	6	10	Visit 1 - V1
36	LV Mass	77.5	g/m2	44	88	Visit 1 - V1
36	Septal Wall Thickness in Diastole	9.0	mm	6	10	Unscheduled Visit
36	LV Mass	89.4	g/m2	44	88	Unscheduled Visit
37	Septal Wall Thickness in Diastole			N/A	N/A	Visit 2 - V2
37	LV Mass			N/A	N/A	Visit 2 - V2
37	Septal Wall Thickness in Diastole	17.0	mm	N/A	N/A	Visit 3 - V3
37	LV Mass	114.6	g/m2	N/A	N/A	Visit 3 - V3
37	Septal Wall Thickness in Diastole	17.0	mm	N/A	N/A	End of Treatment Visit
37	LV Mass	68.7	g/m2	N/A	N/A	End of Treatment Visit
37	Septal Wall Thickness in Diastole	14.5	mm	N/A	N/A	Follow up Visit
37	LV Mass	90.58	g/m2	N/A	N/A	Follow up Visit
37	Septal Wall Thickness in Diastole			N/A	N/A	Visit 1 - V1
37	LV Mass			N/A	N/A	Visit 1 - V1
38	Septal Wall Thickness in Diastole			N/A	N/A	Visit 2 - V2
38	LV Mass			N/A	N/A	Visit 2 - V2
38	Septal Wall Thickness in Diastole	6.0	mm	N/A	N/A	Visit 3 - V3
38	LV Mass	88.6	g/m2	N/A	N/A	Visit 3 - V3
38	Septal Wall Thickness in Diastole	7.9	mm	N/A	N/A	End of Treatment Visit
38	LV Mass	58.45	g/m2	N/A	N/A	End of Treatment Visit
38	Septal Wall Thickness in Diastole	7.3	mm	N/A	N/A	Follow up Visit
38	LV Mass	74.52	g/m2	N/A	N/A	Follow up Visit
38	Septal Wall Thickness in Diastole	6.0	mm	N/A	N/A	Visit 1 - V1
38	LV Mass	62.0	g/m2	N/A	N/A	Visit 1 - V1
38	Septal Wall Thickness in Diastole	10.0	mm	N/A	N/A	Unscheduled Visit
38	LV Mass	83.9	g/m2	N/A	N/A	Unscheduled Visit
38	Septal Wall Thickness in Diastole	8.0	mm	N/A	N/A	Unscheduled Visit
38	LV Mass	93.05	g/m2	N/A	N/A	Unscheduled Visit
39	Septal Wall Thickness in Diastole	9.0	mm	6	10	Visit 2 - V2
39	LV Mass	75.8	g/m2	44	88	Visit 2 - V2
39	Septal Wall Thickness in Diastole	7.0	mm	6	10	Visit 3 - V3
39	LV Mass	61.06	g/m2	44	88	Visit 3 - V3
39	Septal Wall Thickness in Diastole	7.9	mm	6	10	End of Treatment Visit
39	LV Mass	67.78	g/m2	44	88	End of Treatment Visit
39	Septal Wall Thickness in Diastole	8.0	mm	6	10	Follow up Visit
39	LV Mass	58.11	g/m2	44	88	Follow up Visit
39	Septal Wall Thickness in Diastole	13.0	mm	6	10	Visit 1 - V1
39	LV Mass	116.0	g/m2	44	88	Visit 1 - V1
39	Septal Wall Thickness in Diastole	10.0	mm	6	10	Unscheduled Visit
39	LV Mass	96.4	g/m2	44	88	Unscheduled Visit
39	Septal Wall Thickness in Diastole	11.0	mm	6	10	Unscheduled Visit
39	LV Mass	87.6	g/m2	44	88	Unscheduled Visit

During the trial, if the subject recorded a LVEF drop of > 5% from the screening value and/or the subject gained > 2kg/week or ≥ 5% weight from the baseline visit, and/or showed visible edema, the cardiologist performed additional echocardiogram evaluations (including LV mass and SWT measurements) to determine the risk of heart failure due to volume overload.

LVEF = left ventricular ejection fraction; LV Mass = left ventricular mass; SWT = septal wall thickness.



eFigure 8. Average Profiles for A) Left Ventricular Ejection Fraction (Including Unscheduled Visits) and B) Change From Baseline (%) Over Time (Safety Population)

Data are mean ± SD. The criteria for removal of patients from the study were: clinical signs of cardiac failure, LVEF% drops below 50%, or LVEF% shows an absolute drop of >10% from baseline.

CFB = change from baseline; Echo = echocardiogram; LVEF = left ventricular ejection fraction; n = number of patients; SD = standard deviation.