



## Clinical trial results:

### 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

#### Summary

EudraCT number	2018-004405-64
Trial protocol	BE FR DE ES
Global end of trial date	14 September 2020

#### Results information

Result version number	v1 (current)
This version publication date	03 May 2021
First version publication date	03 May 2021

#### Trial information

##### Trial identification

Sponsor protocol code	MT-2-03
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Minoryx Therapeutics BE SA
Sponsor organisation address	Rue Auguste Piccard 48, 6041 Gosselies, Belgium,
Public contact	Sílvia Pascual, Minoryx Therapeutics BE SA, 0034 935441466, spascual@minoryx.com
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Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 October 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 September 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective was to evaluate the effect of 48 weeks' treatment with MIN-102 compared to placebo on cervical spinal cord area as assessed by morphometric MRI measurements. Secondary objectives and exploratory objectives were also evaluated. The secondary objectives included evaluating the effect of 48 weeks of treatment with MIN-102 compared to placebo on: change from baseline in the SARA (Scale for the Assessment and Rating of Ataxia) total score; diffusion tensor imaging (DTI) of the cervical spinal cord; cervical spinal cord total N-acetylaspartate concentration/myo-inositol (tNAA/Mins) ratio (using magnetic resonance spectroscopy [MRS]); MRI quantitative susceptibility mapping (QSM) for iron concentration; dentate nuclei volume; voxel-based analyses (FBA) of the brain; cerebellar composite functional scale (CCFS); fatigue severity scale (FSS); quality of life assessments; clinical and patient global impression of improvement; safety and tolerability of MIN-102.

Protection of trial subjects:

All study patients (caregivers as applicable) were required to read and sign an Informed Consent Form; if the patient was a minor, investigators were required to obtain written informed consent from a parent/legal guardian and written assent from the patient. Consent/assent was obtained prior to any study-specific screening procedures. As part of this procedure, the investigator or an associate would 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 patient/parent was aware of the potential risks, inconveniences, or adverse effects. The parent/legal guardian was informed that the patient could withdraw from the study at any time. In the event of a protocol modification, the Informed Consent Form was to be updated as applicable, with subsequent institutional review board (IRB)/independent ethics committee (IEC) approval and re-consenting of patients.

For optional evaluations of motor evoked potentials and cerebrospinal fluid sampling, additional informed consent and assent was required, which was documented using a check box in the main consent form. In addition, optional consent was required for the collection of results from SARA assessments conducted prior to screening, in patients for whom these data were available. The decision of a patient to participate in these optional assessments or not had no impact on their inclusion in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 7

Worldwide total number of subjects	39
EEA total number of subjects	39

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	14
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 39 patient were enrolled between 02-Apr-2019 (first patient visit) and 14-Sep-2020 (last patient visit) and received treatment with MIN-102 or placebo.

### Pre-assignment

Screening details:

Eleven patients were screened but not enrolled, with 7 patients failing to meet the eligibility criteria, 2 patients withdrawing consent, and 2 patients ineligible due to another reason.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients were randomly assigned to MIN-102 or placebo in a 2:1 ratio using interactive response technology. Controls to maintain the double-blind status included: the oral suspensions containing active drug or placebo were indistinguishable in appearance and taste; the packaging and labeling of the bottles for both treatments was identical; dose adjustment (to achieve the target exposure) was managed by a central unblinded PK expert; random dose adjustments were made for placebo patients.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MIN-102 group

Arm description:

Patients in the MIN-102 group received oral MIN-102 once daily for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	MIN-102
Investigational medicinal product code	
Other name	Leriglitazone hydrochloride
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Patients received oral MIN-102 once daily for 48 weeks using a 10-mL syringe. Initial doses were 150 mg (adult males), 130 mg (adult females), and 2.2 mg/kg (patients  $\geq 12$  to 17 years).

At Visit 1 (after 4 weeks of treatment) blood samples were collected for PK analysis; dosages for individuals were then modified by the PK specialist to achieve the desired plasma exposure of 170  $\mu\text{g}\cdot\text{hr}/\text{mL}$  in each patient. Patients received this dose throughout the study, unless reduction was necessary due to safety or tolerability. Administration could be temporarily interrupted if a patient experienced safety and/or tolerability issues or other conditions that prevented them taking study drug. Treatment was to be stopped if patients showed clinical signs of heart failure, left ventricular ejection fraction changes (drop to below 50% or an absolute drop of  $>10\%$  from baseline), or if indicated after evaluating ECGs following elevations of NT-pro BNP (N-terminal pro B-type natriuretic peptide)  $>300$  pg/mL.

<b>Arm title</b>	Placebo group
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Arm description:

Patients in the placebo group received oral matching placebo once daily for 48 weeks.

Arm type	Placebo
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Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Patients received placebo once daily for 48 weeks using a 10-mL syringe. Random dose adjustments were made for patients receiving placebo in order to maintain the blind.

<b>Number of subjects in period 1</b>	MIN-102 group	Placebo group
Started	26	13
Completed	20	12
Not completed	6	1
Adverse event, non-fatal	4	-
Participation withdrawal by patient/parent/guardia	1	-
Study drug withdrawal by patient/parent/guardian	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	MIN-102 group
Reporting group description:	
Patients in the MIN-102 group received oral MIN-102 once daily for 48 weeks.	
Reporting group title	Placebo group
Reporting group description:	
Patients in the placebo group received oral matching placebo once daily for 48 weeks.	

Reporting group values	MIN-102 group	Placebo group	Total
Number of subjects	26	13	39
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	10	4	14
Adults (18-64 years)	16	9	25
Age continuous			
Units: years			
arithmetic mean	23.1	25.8	-
standard deviation	± 9.79	± 12.67	-
Gender categorical			
Units: Subjects			
Female	11	6	17
Male	15	7	22
Race			
Units: Subjects			
White	20	10	30
Not recorded	6	3	9
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	0	5
Not Hispanic or Latino	15	10	25
Not recorded	6	3	9
Height			
Units: cm			
arithmetic mean	162.8	169.7	-
standard deviation	± 11.78	± 11.60	-
Weight			
Units: kg			
arithmetic mean	58.5	62.1	-
standard deviation	± 17.73	± 16.57	-
Time since genetic diagnosis			
The time (years) since genetic diagnosis of FRDA at date of informed consent. If diagnosis date was partial, then time is difference of years.			
Units: Years			
arithmetic mean	5.16	6.18	-
standard deviation	± 4.458	± 4.977	-
Time since onset of symptoms			
The time (years) since the onset of FRDA symptoms at date of informed consent. If symptoms date was			

partial, then time is difference of years.			
Units: Years			
arithmetic mean	9.63	12.27	
standard deviation	$\pm 5.146$	$\pm 8.081$	-
Age at onset of symptoms			
The age of the patient at the onset of symptoms. If the symptoms date was partial, then time is difference of years.			
Units: Years			
arithmetic mean	14.2	14.3	
standard deviation	$\pm 7.50$	$\pm 7.81$	-

## End points

### End points reporting groups

Reporting group title	MIN-102 group
Reporting group description:	
Patients in the MIN-102 group received oral MIN-102 once daily for 48 weeks.	
Reporting group title	Placebo group
Reporting group description:	
Patients in the placebo group received oral matching placebo once daily for 48 weeks.	

### Primary: Change from Baseline in spinal cord area cervical segment C2-C3

End point title	Change from Baseline in spinal cord area cervical segment C2-C3
End point description:	
Values provided here are the least squares (LS) mean (standard error [SE]) change from Baseline to Week 48 area in measurements of spinal cord cervical segment C2-C3 area, estimated from the MRI T1-weighted brain image for the modified intent-to-treat (mITT) population. The mITT consisted of all patients 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. There was no conclusive outcome from the primary objective to evaluate the change from Baseline in cervical spinal cord area after 48 weeks of treatment. In both treatment groups, there was no clinically meaningful change in area from Baseline to Week 48; numerical differences between the groups (a small decrease in the area in the MIN-102 group [least squares (LS) mean change -0.394 mm <sup>2</sup> ] and a small increase in the placebo group [0.076 mm <sup>2</sup> ]) were not considered to be clinically relevant.	
End point type	Primary
End point timeframe:	
Baseline to Week 48	

End point values	MIN-102 group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 <sup>[1]</sup>	12 <sup>[2]</sup>		
Units: mm <sup>2</sup>				
least squares mean (standard error)	-0.39420 ( $\pm$ 0.55483)	0.07648 ( $\pm$ 0.71655)		

Notes:

[1] - Two patients in the mITT population did not undergo MRI at both baseline and Week 48.

[2] - All patients in the mITT population underwent MRI at both baseline and Week 48.

### Statistical analyses

Statistical analysis title	Primary endpoint analysis
Comparison groups	Placebo group v MIN-102 group
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.608 <sup>[3]</sup>
Method	ANCOVA



Notes:

[3] - P value for the difference between treatment arms in the mITT population.

## Secondary: Change from Baseline in MRI QSM for iron concentration

End point title	Change from Baseline in MRI QSM for iron concentration
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End point description:

This secondary efficacy endpoint evaluated the effect of 48 weeks of treatment with MIN-102 compared to placebo on magnetic resonance imaging (MRI) quantitative susceptibility mapping (QSM) for iron concentration. Values reported here are for the mITT population. At Baseline, the mean iron concentration was comparable in the MIN-102 and placebo groups (64.89 ppb and 73.86 ppb, respectively). The LS mean change from Baseline to 48 weeks saw little change in the MIN-102 group (increase of 0.098 ppb), with an increase of 4.858 ppb in the placebo group.

End point type	Secondary
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End point timeframe:

Baseline to Week 48

End point values	MIN-102 group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17 <sup>[4]</sup>	9 <sup>[5]</sup>		
Units: parts per billion				
least squares mean (standard error)	0.09757 ( $\pm$ 1.32894)	4.85848 ( $\pm$ 1.84216)		

Notes:

[4] - Five patients in the mITT population did not undergo QSM assessment at both baseline and Week 48.

[5] - Three patients in the mITT population did not undergo QSM assessment at both baseline and Week 48.

## Statistical analyses

Statistical analysis title	Secondary efficacy endpoint analysis
Comparison groups	Placebo group v MIN-102 group
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.05 <sup>[6]</sup>
Method	ANCOVA

Notes:

[6] - P value for the difference between treatment arms in the mITT population.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were recorded from Baseline until the Follow-up Visit, which occurred 28 +/-5 days after the last dose of study drug.

Adverse event reporting additional description:

TEAEs were defined as AEs occurring on or after the first dose of study treatment. Adverse events that were recorded more than twice in any group are reported here.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	MIN-102 group
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Reporting group description:

Patients in the MIN-102 group received oral MIN-102 once daily for 48 weeks.

Reporting group title	Placebo group
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Reporting group description:

Patients in the placebo group received oral matching placebo once daily for 48 weeks.

Serious adverse events	MIN-102 group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Dilatation atrial			
subjects affected / exposed	1 / 26 (3.85%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.35 %

Non-serious adverse events	MIN-102 group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	13 / 13 (100.00%)	
Vascular disorders			
Hot flush			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 4	0 / 13 (0.00%) 0	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	8 / 26 (30.77%)	0 / 13 (0.00%)	
occurrences (all)	13	0	
Fatigue			
subjects affected / exposed	10 / 26 (38.46%)	3 / 13 (23.08%)	
occurrences (all)	14	3	
Generalised oedema			
subjects affected / exposed	2 / 26 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	5	0	
Oedema peripheral			
subjects affected / exposed	19 / 26 (73.08%)	0 / 13 (0.00%)	
occurrences (all)	44	0	
Peripheral swelling			
subjects affected / exposed	4 / 26 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	8	0	
Pyrexia			
subjects affected / exposed	4 / 26 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	6	1	
Swelling face			
subjects affected / exposed	3 / 26 (11.54%)	0 / 13 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 26 (19.23%)	4 / 13 (30.77%)	
occurrences (all)	6	5	
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	4	
Oropharyngeal pain			
subjects affected / exposed	5 / 26 (19.23%)	3 / 13 (23.08%)	
occurrences (all)	7	3	
Investigations			

Blood cholesterol increased		
subjects affected / exposed	5 / 26 (19.23%)	1 / 13 (7.69%)
occurrences (all)	5	1
Blood creatine phosphokinase increased		
subjects affected / exposed	4 / 26 (15.38%)	1 / 13 (7.69%)
occurrences (all)	4	1
Haemoglobin decreased		
subjects affected / exposed	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	3	0
Haemoglobin increased		
subjects affected / exposed	2 / 26 (7.69%)	3 / 13 (23.08%)
occurrences (all)	2	3
Lymphocyte count increased		
subjects affected / exposed	2 / 26 (7.69%)	3 / 13 (23.08%)
occurrences (all)	3	3
Mean cell haemoglobin concentration decreased		
subjects affected / exposed	1 / 26 (3.85%)	2 / 13 (15.38%)
occurrences (all)	1	3
N-terminal prohormone brain natriuretic peptide increased		
subjects affected / exposed	8 / 26 (30.77%)	0 / 13 (0.00%)
occurrences (all)	9	0
Neutrophil count decreased		
subjects affected / exposed	3 / 26 (11.54%)	3 / 13 (23.08%)
occurrences (all)	7	6
Red blood cell count decreased		
subjects affected / exposed	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	4	0
Urine cytology abnormal		
subjects affected / exposed	3 / 26 (11.54%)	1 / 13 (7.69%)
occurrences (all)	5	1
Urine output increased		
subjects affected / exposed	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	3	0
Weight increased		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 26 (46.15%)</p> <p>15</p> <p>4 / 26 (15.38%)</p> <p>10</p>	<p>2 / 13 (15.38%)</p> <p>2</p> <p>2 / 13 (15.38%)</p> <p>3</p>	
<p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 26 (15.38%)</p> <p>9</p>	<p>4 / 13 (30.77%)</p> <p>7</p>	
<p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Paraesthesia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 26 (11.54%)</p> <p>3</p> <p>16 / 26 (61.54%)</p> <p>34</p> <p>1 / 26 (3.85%)</p> <p>4</p>	<p>3 / 13 (23.08%)</p> <p>5</p> <p>5 / 13 (38.46%)</p> <p>12</p> <p>1 / 13 (7.69%)</p> <p>1</p>	
<p>Blood and lymphatic system disorders</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 26 (11.54%)</p> <p>3</p>	<p>0 / 13 (0.00%)</p> <p>0</p>	
<p>Eye disorders</p> <p>Eyelid oedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lacrimation increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 26 (15.38%)</p> <p>7</p> <p>3 / 26 (11.54%)</p> <p>4</p>	<p>0 / 13 (0.00%)</p> <p>0</p> <p>0 / 13 (0.00%)</p> <p>0</p>	
<p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p>	<p>3 / 26 (11.54%)</p> <p>3</p>	<p>1 / 13 (7.69%)</p> <p>1</p>	

subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5	2 / 13 (15.38%) 2	
Vomiting subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5	1 / 13 (7.69%) 2	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 5	0 / 13 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 7	2 / 13 (15.38%) 3	
Back pain subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	3 / 13 (23.08%) 5	
Neck pain subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5	0 / 13 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	3 / 13 (23.08%) 4	
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 13 (7.69%) 4	
Influenza subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 7	2 / 13 (15.38%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 26 (30.77%) 10	6 / 13 (46.15%) 9	
Rhinitis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 4	2 / 13 (15.38%) 3	
Metabolism and nutrition disorders			

Vitamin B12 deficiency subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	0 / 13 (0.00%) 0	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2019	Protocol amendment: v2.0 <ul style="list-style-type: none"><li>Update of prohibited concomitant medications.</li></ul>
31 October 2019	Protocol amendment: v3.0 <ul style="list-style-type: none"><li>Clarification of discontinuation criteria in case of NT-pro BNP elevations for participant safety.</li><li>Clarification of requirements of the End of Treatment visit.</li></ul>
25 February 2020	Protocol amendment: v4.0 <ul style="list-style-type: none"><li>Addition of exploratory objectives with recorded MRI data, including analysis of further brain regions.</li><li>Addition of main metabolite M3 to PK analysis.</li><li>Change of statistical analysis of the primary endpoint from a 2-sample t-test to an analysis of covariance (ANCOVA) model.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported