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A study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of MTL-CEBPA in children with mucopolysaccharidosis type IH

Submission date
14/09/2022

Recruitment status
No longer recruiting

Registration date
24/02/2023

Overall study status
Completed

Last Edited
18/04/2023

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Mucopolysaccharidosis type IH (MPS1H or Hurler Syndrome) is an incurable rare genetic condition that occurs both in males and females. It is caused by a lack of an enzyme (α-L-iduronidase) resulting in the accumulation of certain sugars in many organs, including the skeleton, heart, and respiratory systems, and if untreated leads to early death. There is still a high, unmet medical need for improved treatment of MPS1H. This study investigates the safety of a 'small activating RNA' treatment called MTL-CEBPA (which is not yet approved by regulatory authorities) given as a 30-minute intravenous infusion in children with MPS1H to establish a dose which is both well tolerated and boosts the production of the α-L-iduronidase enzyme.

Who can participate?
Children aged 12 to 16 years inclusive will be recruited into Cohort 1, and children aged 4 to 11 years will be recruited into Cohort 2. All children will have successfully undergone an allogeneic haematopoietic stem cell transplantation (bone marrow transplant) at least 6 months previously.

What does the study involve?
Three increasing single-dose levels of MTL-CEBPA will be investigated. The optimum dose will then be given at either 2-, 3- or 4-weekly intervals for 6 months. The chosen dosing interval will be determined from the single dose phase. At the end of the 6 months of treatment, children who appear to have benefitted and had no significant side effects can choose to continue receiving long-term treatment in an open-label extension. During the study, patients will undergo assessments which include physical examinations, cognitive, motor and behavioural assessments, blood, urine, x-rays, electrocardiogram, ultrasound, walking and breathing tests. Children and their families will also be asked to complete questionnaires about their day-to-day experience of living with MPS1H.

What are the possible benefits and risks of participating?
As with all clinical studies of drugs in development, participants may experience adverse

reactions to the study experimental drug. Individual drug-specific precautions with regard to participant eligibility, dose modifications and stopping rules have been implemented in the protocol to minimise potential risks to participants. Participants will be carefully monitored for adverse events at each visit and by telephone after the study. Participants will be informed of the known side effects of all study drugs prior to agreeing to take part in the study and will be informed as and when new information becomes available.
Participants may experience some discomfort, lightheadedness and bruising while giving blood. There is a rare chance of infection at the blood sample site. Blood will be taken by an appropriately qualified healthcare professional and a local anaesthetic gel will be used to minimise the pain. The total blood volume to be taken over 5-8 weeks is 111.0 ml. This is a considerable amount of blood to take from small children. Parents will be encouraged to keep an eye on their child after a blood draw.
Removal of the sticky pads used during the electrocardiogram (ECG) may also cause slight discomfort. Caution is used by the trained personnel conducting this procedure to minimise the discomfort when removing the sticky pads.
The administration route for study treatment may cause discomfort, irritation, mild bruising, bleeding and rarely, infection. MTLCEBPA is an RNA-based drug and therefore there is a possibility that participants may develop anti-drug antibodies (ADAs).
Participants will be offered transportation and accommodation as needed through a specialised agency which is experienced in dealing with MPS-1H.
The study drug might have adverse effects on an unborn child. Furthermore, it is not known if the study drug has transient effects on the composition of sperm.
Participants over 12 years of age should be educated on acceptable contraception and the importance of compliance. To participate in the trial, participants of childbearing potential must adhere to the contraception requirement (specified in the study protocol).
If a participant inadvertently becomes pregnant during the study, the participant will be immediately discontinued from study intervention.
The planned radiation exposures (radiographs of the pelvis and hips) are appropriate for the purposes of this study, and there is no practical alternative that would avoid exposure to ionising radiation. Radiographs of the pelvis and hips are part of normal standard care for children with this condition, but participants in this trial may have these radiographs taken more often than would be clinically necessary. However, some flexibility has been incorporated into the protocol to mitigate this, allowing the initial radiograph to be omitted if one has been recently taken for clinical reasons. The risks to the participant are small and there may be benefits in early diagnosis of hip dysplasia or other complications.

Where is the study run from?
Manchester University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2022 to April 2025

Who is funding the study?
MiNA Alpha Ltd (UK)

Who is the main contact?
Joanna Nicholls, joanna@minatx.com

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-001379-15

Integrated Research Application System (IRAS)
1005674

Protocol serial number
MNA-3521-016, IRAS 1005674, CPMS 52775

Study information

Scientific Title
An open-label, Phase I/II, non-comparative, clinical study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of MTL-CEBPA in paediatric participants with mucopolysaccharidosis type 1H (MPS1H, Hurler Syndrome) (SMART in MPS1H)

Acronym
SMART in MPS-IH

Study objectives
Primary objective:
To investigate the safety and tolerability of MTL CEBPA following single and multiple dosing of MTL CEBPA in paediatric participants with MPS 1H.

Secondary objectives:
1. To assess the pharmacodynamic (PD) effects of MTL CEBPA following single and multiple dosing of MTL CEBPA in paediatric participants with MPS 1H.
2. To assess the pharmacokinetic (PK) concentrations of CEBPA-51 in plasma and circulating white blood cells (WBC) following single and multiple dosing of MTL CEBPA in paediatric participants with MPS 1H.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/11/2022, Hampstead Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, UK; +44 (0)207 104 8345/+44 (0)207 104 8189; hampstead.rec@hra.nhs.uk), ref: 22/LO/0665

Study design
Non-randomized study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mucopolysaccharidosis type 1H (MPS1H) (Hurler Syndrome)

Interventions

This is a non-randomized study (each sequentially enrolled participant will receive at least one dose of IMP) of two cohorts and two phases.
Cohort 1 will include six participants aged ≥12-15 years (at screening)
Cohort 2 will include six participants aged ≥4-11 years (at screening)

Phase 1 Cohort 1 (this cohort will be treated before dosing participants in Cohort 2):
Two participants will receive a single dose of IMP of 0.5 mg/kg
Two participants will receive a single dose of IMP dose of 1.5 mg/kg
Two participants will receive a single dose of IMP of 3.5 mg/kg

Phase 1 Cohort 2:
Two participants will receive a single dose of IMP of 0.5 mg/kg
Two participants will receive a single dose of IMP dose of 1.5 mg/kg
Two participants will receive a single dose of IMP of 3.5 mg/kg

In Cohort 1, the first two participants will receive the lowest dose of MTL CEBPA (low dose, 0.5 mg/kg). Once the safety data from 4 weeks post-dose have been reviewed from both participants and the dose is deemed (by the Investigator and Sponsor's Medical Monitor) to have been tolerated, the next two participants will receive a higher dose of MTL CEBPA (mid dose, planned to be 1.5 mg/kg). After at least 4 weeks follow-up, and again assuming the dose is deemed to be tolerated, the remaining two participants will receive the highest dose of MTL CEBPA (high dose, planned to be 3.5 mg/kg). At each dose level, there will be a minimum of 24 hours between the first participant being dosed and the second participant being dosed.

The IMP is MTL-CEBPA is diluted into 50 ml 0.9% Normal Saline for intravenous use and administered via infusion pump intravenously into a peripheral or central line over 30 minutes. It is a chemically synthesised double-stranded CEBPA-51 saRNA targeting the CEBPA promoter, encapsulated into specialised liposomes also known by the registered trade name SMARTICLES®.

Phase 2 multiple dosing:
The outcome of the single-dose phase will determine the dosing regimen investigated in the multiple-dose phase for each cohort.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
MTL-CEPBA

Primary outcome(s)
Safety (primary): Safety will be assessed by monitoring of AEs graded according to toxicity criteria (CTCAE v5.0), measurement of vital signs (inc. blood pressure, pulse, body temperature, and respiratory rate), 12-lead electrocardiograms (ECGs) and safety laboratory data (including. haematology, coagulation, clinical chemistry, urinalysis, and complement activation [complement fragments C3a and Bb]). Chimerism will also be routinely assessed. A description of both participant and investigator assessment of tolerability will be collected. AEs will be collected throughout the study, from informed consent until the end of study visit. All other

measurements will be taken from the screening visit, all the way through the study at set study visits and at the follow-up/early termination visit.

Key secondary outcome(s))

1. Pharmacodynamic analysis of the study drug MTL-CEBPA: measured using blood samples and urine samples collected at baseline visit and at every visit until the end of the study. PD assessments will include IDUA enzyme activity, amounts of IDUA mRNA, IDUA protein in macrophages/monocytes, peripheral CD 34+ cells and plasma. Concentrations of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate in plasma and urine will also be assessed. Tumor necrosis factor α (TNFα) will also be assessed.
2. Pharmacokinetic analysis of the study drug MTL-CEBPA: plasma and circulating WBC concentrations of CEBPA 51 will be analysed using hybridization-based high-performance liquid chromatography (HPLC) assay in order to determine the PK properties of CEBPA 51 after IV administration of MTL CEBPA. Blood samples will be collected on Weeks 1, 2, 3, 4, 5 (Phase 1 all participants); 7, 9, 11, 13 (Phase 2 QW4 dosing); 7, 9, 11, 13,15, 17 (Phase 2 QW3 dosing); 7, 8, 9, 10, 12, 16 (Phase 2 QW2 dosing).

All measurements will be taken from the screening visit, all the way through the study at set study visits and at the follow-up/early termination visit.

Exploratory:
Clinical outcome/performance assessments will include:
1. Spirometry: forced vital capacity [FVC] and forced expiratory volume in the first second [FEV1]) measured using a spirometer at baseline and at the end of the study
2. Left ventricular ejection fraction/fractional shortening/posterior wall thickness/septum wall thickness/end-systolic diameter/end-diastolic diameter and ejection fraction modified Simpson's measured using non-invasive echocardiogram at baseline and at the end of the study
3. X-ray of hips and pelvis to measure at a minimum acetabular index, migration percentage, Smith ratio and neck-shaft angle at baseline and at the end of the study
4. 6-minute walk test: measurement of the distance that the participant can walk in 6 minutes on a hard flat surface (only for participants aged 6 years and above who are able to follow instructions) at baseline and at the end of the study
5. Shoulder joint mobility measured using goniometry of joint mobility in both shoulders (JROM) at baseline and at the end of the study
6. Measurement of paediatric gait arms legs spine using the Paediatric Gait Arms Legs Spine Toolkit (pGALSPlus) at baseline and at the end of the study
7. Fine manual control, manual coordination, body coordination, strength and agility measured using the Bruininks-Oseretsky Test of Motor Proficiency (fine motor and gross motor) at baseline and at the end of the study
8. Manual dexterity and hand function measured using the 9 Hole Peg Test at baseline and at the end of the study
9. Visual-motor deficits measured using the Beery-Buktenica Developmental Test of Visual-Motor Integration (6th Edition) at baseline and at the end of the study
10. Non-verbal visual processing speed measured using the Processing Speed Index from the Wechsler Intelligence Scale for Children, 5th Edition or Wechsler Preschool and Primary Scale of Intelligence, 4th Edition, at baseline and at the end of the study
11. Accurate spatiotemporal parameters of gait measured using a Zeno™ walkway at baseline and at the end of the study
12. Self-administered measurement of the level of pain using the Pain Faces Scale (Wong-Baker) after completion of the 6-minute walk test at baseline and at the end of the study
13. Anti-drug antibodies against IDUA and MTL-CEBPA measured using blood samples (retrospective analysis of stored frozen samples)

14. Observer (parent/guardian) reported outcome assessment using the Paediatric Quality of Life Inventory – Pain Module (PedsQL) at baseline and at the end of the study
15. The impact of paediatric acute and chronic health conditions on the parents and family, measured using the Paediatric Quality of Life Inventory – Family Impact Module (PedsQL) at baseline and at the end of the study
16. Severity of the participant's disease measured using the Clinical Global Impression S (CGI-S) at baseline
17. Improvement from baseline in the participant's disease measured using the Clinical Global Impression I (CGI-I) at the end of the study

Completion date
30/04/2025

Eligibility

Key inclusion criteria
1. Verbal assent will be obtained from the participant as well as written informed consent from the parent/legal guardian prior to any study specific procedure
2. Male or female participants aged ≥12-16 years (Cohort 1), or ≥4-11 years (Cohort 2) with a biochemical and genetic diagnosis of MPS-1H
3. Minimum 6 months post HSCT
4. Off immunosuppression, including corticosteroids for at least 4 weeks prior to study
5. Stable myeloid chimerism (>80% donor cells as determined by short tandem repeats [STR] in <PBMCs>)
6. Anticipated life expectancy in excess of the study period
7. Not enrolled in any other interventional study
8. Acceptable laboratory parameters , consistent with participant age and MPS-1H diagnosis
9. Negative blood pregnancy test for females of childbearing potential within 10 days prior to the first drug administration
10. For female participants of child-bearing potential, agreement to be abstinent or use highly effective contraception (defined as method(s) that result in a failure rate of <1% per year) in females of childbearing potential during the entire study and defined post-study period
11. Willingness and ability to comply with all protocol requirements including scheduled visits, treatment plans, laboratory tests and other study procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
4 years

Upper age limit
16 years

Sex

All

Key exclusion criteria
1. Participants who received investigational drug(s) within the last 30 days (or 5 half-lives if longer) prior to study treatment initiation
2. Participants receiving laronidase at commencement of study (minimum 6 weeks wash out)
3. Major surgery within the last 30 days prior to study treatment initiation, or planned within the study period
4. Pregnant or lactating women
5. Known hypersensitivity to the active substance (MTL-CEBPA) or to any of the excipients, not managed by conventional approaches. Excipients include: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC); 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE); Cholesteryl hemisuccinate (CHEMS); and Cholesteryl-4-[[2-(4-morpholinyl)ethyl]amino]-4-oxobutanoate (MOCHOL)
6. Any other condition (e.g., known or suspected poor compliance, etc.) that, in the judgment of the investigator, may affect the participant’s ability to follow the protocol specific procedures

Date of first enrolment
01/08/2023

Date of final enrolment
28/02/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
MiNA Therapeutics Ltd

Funder(s)

Funder type
Industry

Funder Name
MiNA Alpha Ltd

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No