Integrated Prospective and Retrospective Observational Study to Characterize Biomarkers and Disease Progression in Patients with Pelizaeus-Merzbacher disease

Published: 24-08-2022
Last updated: 19-04-2025

Primary objectives:To prospectively assess longitudinal changes in Proteolipid Protein 1 (PLP1) and additional disease-related biomarkers in cerebral spinal fluid (CSF) and blood and evaluate their utility in support of the development of therapies...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON51633

Source
ToetsingOnline

Brief title
NH00005

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Demyelinating disorders

Synonym
leukodystrophy, Pelizaeus-Merzbacher disease, white matter disease

Research involving
Human

Sponsors and support

Primary sponsor: Ionis Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Ionis Pharmaceuticals

Intervention

Keyword: biomarkers, Observational Study, Pelizaeus-Merzbacher disease

Outcome measures

Primary outcome

Primary Endpoints

Fluid Biomarkers

CSF, plasma, serum, whole blood and a blood spot collected from participants with PMD at a minimum of 2 time points at Week 1, and Week 53. Biofluid collection at Week 106 is optional. Biofluids will be analyzed for biomarker levels that may include, but are not limited to:

• Changes in PLP1 in CSF

• Disease-related biomarkers in CSF and/or blood may include but are not limited to:

- proteins potentially associated with PLP1 in CSF, serum, and plasma

- Measures of neurodegeneration: neurofilament light (NfL), phosphorylated neurofilament heavy (pNfH), n-acetylaspartate (NAA), n-acetylaspartylglutamate (NAAG), visinin-like protein 1(VILIP1)

- Measures of myelin: myelin basic protein (MBP), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), 2*,3*-Cyclic nucleotide 3*-phosphodiesterase (CNP), sphingolipids (e.g.,

sphingomyelin), galactocerebrosidase (GalC), sulfatide, Insulin-like growth factor 1 (IGF-1), growth hormone

- Measures of neuroinflammation: chemokine ligand 3 (CCL3), chemokine ligand 8 (CCL8), tumor necrosis factor-alpha (TNF-α), interlukin-6 (IL-6), c-x-c motif chemokine 5 (CXCL5), chemokine ligand 2 (CCL2), c-x-c motif chemokine ligand 10 (CXCL10), chitinase-3 like protein (YKL40), s100 calcium-binding protein b (S100b), glial fibrillary acidic protein (GFAP), 8-Isoprostane (8 isoPGF2α), ionized calcium binding adaptor molecule (1Iba-1)

Neuroimaging

Neuroimaging assessments will be performed at a minimum of 2 time points at Week 1 and Week 53. Neuroimaging at Week 106 is optional.

• Analysis of changes in neuroimaging parameters may include but are not limited to:

- Regional brain volumes (T1-weighted, T2-weighted, fluid-attenuated inversion recovery [FLAIR] magnetic resonance imaging [MRI])
- Diffusivity and fractional anisotropy, myelin water imaging (MWI) and neurite orientation dispersion and density imaging (NODDI) (diffusion tensor imaging [DTI])
- Brain metabolites (magnetic resonance spectroscopy [MRS])

Clinical Assessments:

Changes in performance on clinical outcome assessments and patient and

caregiver-reported outcomes will be evaluated in all participants, regardless of their chronological age, will be analyzed for the following:

• Changes across clinical outcome assessments for all participants:

- Cailloux PMD scoring

- Gross Motor Function Classification System Expanded & Revised (GFMCS E&R)

- Gross Motor Function Classification System in Metachromatic Leukodystrophy (GFMC-MLD)

- Modified Ashworth Scale

- Bayley Scales of Infant and Toddler Development, 3rd Edition (BSDI-III)

- Electrophysiological Assessment

- Leiter 3rd Edition (Leiter 3)

- Eating and Drinking Ability Classification System (EDACS)

- Manual Ability Classification System (MACS)

- Gross Motor Function Measure (GMFM)

• Changes across patient and caregiver-reported outcomes:

- Vineland Adaptive Behavior Scales, 3rd Edition (Vineland-3)

- Most Bothersome Symptoms (MBS)

- Pediatric Quality of Life Inventory (PedsQL*)

- EuroQuol Five Dimensions Questionnaire Youth (EQ-5D-Y)

- Composite Sleep Disturbance Index (CSDI)

Associations between neuroimaging, clinical assessments, and fluid biomarkers

may be evaluated.

Secondary outcome

Secondary Endpoints

The clinical presentation and disease course of patients with PMD will be evaluated through a retrospective chart review. Retrospective analysis may include, but is not limited to:

• Evaluation of the onset and progression of PMD manifestations (i.e., change over time in symptoms, signs, neuroimaging, and laboratory findings as available) before a confirmed diagnosis of PMD

• Evaluation of the post-PMD diagnosis disease progression (i.e., change over time in symptoms, signs, neuroimaging, and laboratory findings as available)

To characterize health services utilization and economic and disease burden for the patients and caregiver(s), analysis may include, but is not limited to:

• Utilization of health services including medical history, family history, hospitalizations, medical treatment, genetic diagnoses, clinical assessments, laboratory results, neuroimaging results and data (see Section 6.2.1), extracted from medical records as part of the retrospective chart review and collected during the prospective study.

• Changes across caregiver impact will be analyzed for the following:

- Caregiver Impact Questionnaire (CIQ)

- Work Productivity and Activity Impairment Questionnaire (WPAI)

Study description

Background summary

Neurons are a special type of cell in the brains and spinal cord that transmit and receive electric signals (impulses) throughout the central nervous system. Neurons are covered in myelin. Myelin serves an incredibly important function. It protects the axon and allows an impulse to get from one neuron to another. The protein called *proteolipid protein 1* (PLP1) plays an important role in the formation of myelin. In PMD the protein PLP1 has abnormalities and causes little or no myelin to be formed. This results in little, if any, impulse making it to the next neuron, which causes problems in the nervous system of the patient.

Study objective

Primary objectives:
To prospectively assess longitudinal changes in Proteolipid Protein 1 (PLP1) and additional disease-related biomarkers in cerebral spinal fluid (CSF) and blood and evaluate their utility in support of the development of therapies for PMD.

To prospectively assess longitudinal changes in neuroimaging parameters relevant to PMD, including but not limited to myelination and white matter atrophy.

To prospectively assess longitudinal changes in performance on clinical, and patient and caregiver-reported outcome assessments to inform development of therapies for PMD.

Secondary objectives:

To characterize health services utilization and economic and disease burden for the patients and caregiver(s).

To perform a retrospective chart review of the patient*s medical history and family history to characterize the natural history (NH) of PMD since birth.

To identify associations that may be potential predictors of pathological and clinical progression in PMD.

Study design

This is a multi-center, non-randomized, non-interventional integrated

prospective and retrospective study in participants with PMD who are able to undergo general anesthesia or conscious sedation to collect fluid biomarkers (CSF and blood), neuroimaging, and clinical assessments to be used in support of the development of therapies for PMD.
Up to 5 sites worldwide will participate in this study.
Approximately 20 participants who have a diagnosis of Pelizaeus-Merzbacher Disease with genetic confirmation of PLP1 duplication will be enrolled into this study.

Prospective Study
Each participant will undergo a minimum of 2 CSF collections and neuroimaging procedures, at the Baseline visit and Week 53 visit. A third CSF collection and neuroimaging procedure may be performed at the Week 106 visit if feasible.
Prior to each CSF collection and neuroimaging procedure, participants and their caregivers will complete standardized clinical, patient and caregiver assessments, conducted over multiple calendar days (if needed). A subset of patient and caregiver reported outcome assessments will be administered remotely approximately every 6 months.
Participants not completing at least 2 CSF collection or neuroimaging procedures may be replaced. Up to 40 participants may be enrolled.
Twenty-four (24) hours following each CSF collection procedure, follow-up contact (via telephone call or in person) from the Study Center will be made to the participant's caregiver for a safety assessment.
The study duration for each participant will be up to 26 months.

Retrospective Study
Each participant*s medical and family history data will be collected retrospectively from available medical notes and charts, from birth up to the end of the study period. Data collected may include but is not limited to medical and treatment history, family history, age at onset and diagnosis, clinical assessments, hospitalizations, procedures, genetic diagnoses, and laboratory assessments. These data will be collected by qualified site personnel with expertise in PMD and entered in the study database during the prospective study. The retrospective study will only collect data from participants registered in the study.

Study burden and risks

The patient will need to visit the study center 4 times during the whole study, which will last 26 months. These are a screening visit and 3 visits during the study, in week 1, 53 and 106.

Blood draws:
Blood draws will be performed 4 times at the visits at the study center (screening, week 1, 53, 106). At every occasion 2-6 ml blood will be drawn, depending on the weight of the child. In total the maximum volume for blood draws will be approximately 47ml during the whole study.

MRI / MRS:
At studies visits in week 1, 53 and 106 MRI/MRS will be performed on the patient.

Lumbar puncture for brain fluid collection:
At least 2 lumbar puncture will be performed during the whole study to collect brain fluid. These lumbar punctures will be performed during the study visit in week 1 and 53. In week 106 an additional optional lumbar puncture might be performed.

ECG:
During the screening visit an ECG will be performed. No further ECGs are planned during the study.

Contacts

Public
Ionis Pharmaceuticals, Inc.

2855 Gazelle Court 2855 Gazelle Court
Carlsbad CA 92010
US
Scientific
Ionis Pharmaceuticals, Inc.

2855 Gazelle Court 2855 Gazelle Court
Carlsbad CA 92010
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Key Inclusion Criteria
1. Participant has a parent or caregiver capable of providing informed consent (signed and
dated) and able to attend all scheduled study visits and provide feedback regarding the
participant*s symptoms and performance as described in the protocol and be able to
comply with all study requirements
2. Participant has a diagnosis of Pelizaeus-Merzbacher Disease with genetic confirmation of
PLP1 duplication
3. Male, 6 months-8 years old, inclusive, at the time of informed consent and phenotype
consistent with classic PMD
4. No contraindications for LP*s, blood draws, neuroimaging, sedation (if necessary) or
other study procedures
5. Medically stable who can undergo sedation or general anesthesia

Exclusion criteria

Key Exclusion Criteria
Clinically significant abnormalities in medical history (e.g., clinically significant renal,
hepatic, or cardiac abnormalities; systemic infection within 3 months of Screening; major
surgery within 3 months of Screening) or physical examination
2. Phenotype consistent with SPG2
3. Unwillingness or inability to comply with study procedures, including follow-up, as
specified by this protocol, or unwillingness to cooperate fully with the Investigator
4. Any contraindications or unwillingness to undergo a LP, including but not limited to:
a. Platelet count < 100,000/µL
b. International normalized ratio (INR) > 1.4
c. Prothrombin time (PT) or partial thromboplastin time (PTT) > upper limit of normal
(ULN)
d. History of bleeding disorder
e. Use of Warfarin
f. Suspected raised intracranial pressure as determined by the Investigator

g. Suspected spinal epidural abscess as determined by the Investigator
h. History of intolerance to the LP procedures (e.g., severe headache) as determined by
the Investigator
i. Evidence of infection at the anticipated LP site as determined by the Investigator
j. Significant lower spinal deformity, prior spinal fusion surgery, or other spinal surgery
at LP site
5. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B
diagnosed by initial serological testing and confirmed with ribonucleic acid (RNA)
testing, or prior treatment for hepatitis C. Patients at Screening who test positive by
serology, but negative by RNA may be allowed by the Investigator in consultation with
the Sponsor medical monitor
6. LP procedure 30 days or less before the CSF collection visit
7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or
carcinoma in situ of the cervix that has been successfully treated. Patients with a history
of other malignancies that have been treated with curative intent and which have no
recurrence within 5 years may also be eligible if approved by the Sponsor medical
monitor
8. Treatment with another investigational drug, gene therapy, stem cell therapy, biological
agent, or device within 30 days of Screening, or 5 half-lives of investigational agent,
whichever is longer
9. Previous treatment with an oligonucleotide (including siRNA) within 4 months of screening if single dose received, or within 12 months of Screening if multiple doses received. This exclusion does not apply to vaccines (both mRNA and viral vector vaccines).
10. History of severe allergic or anaphylactic reactions or other adverse reactions to anesthetics used in this study
11. Active bacterial or viral infection
12. Have any other conditions, which, in the opinion of the Investigator would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-11-2022
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	24-08-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL79612.029.22