A Phase 1/2 Open-Label, Multicenter, Dose Ranging and Confirmatory Study to Assess the Safety, Tolerability and Efficacy of PBKR03 Administered to Pediatric Subjects with Early Infantile Krabbe Disease (Globoid Cell Leukodystrophy) (GALax-C)

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Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON51988

Source
ToetsingOnline

Brief title
Study of Safety, Tolerability and Efficacy of PBKR03

Condition

- Metabolic and nutritional disorders congenital
- Demyelinating disorders

Synonym

Early Infantile Krabbe Disease, Globoid Cell Leukodystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Passage Bio, Inc.
Source(s) of monetary or material Support: Passage Bio;Inc.

Intervention

Keyword: Early Infantile Krabbe Disease, gene therapy, Globoid Cell Leukodystrophy, hereditary metabolic disease

Outcome measures

Primary outcome

To assess the safety and tolerability of PBKR03

Secondary outcome

To assess the efficacy of PBKR03

To assess the pharmacokinetics of PBKR03

To assess the effects of PBKR03 on pharmacodynamic and disease biomarkers

To assess the effects of PBKR03 on disease progression

To assess the effects of PBKR03 on quality of life and healthcare resource

utilization

Study description

Background summary

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disease (LSD) caused by mutations in the gene encoding the hydrolytic enzyme galactosylceramidase (galactocerebrosidase; GALC; EC#3.2.1.46; Wenger et al 2000). This enzyme is responsible for the degradation of certain galactolipids, including galactosylceramide (ceramide) and galactosylsphingosine (psychosine). In Krabbe disease, GALC deficiency causes

toxic accumulation of psychosine in the lysosomes of cells throughout the nervous system (Svennerholm et al 1980). The myelin-producing oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) are particularly sensitive to the accumulation of psychosine, resulting in widespread death of these cells. The resulting myelin breakdown in both the CNS and PNS is accompanied by reactive astrocytic gliosis and the infiltration of giant multinucleated macrophages (*globoid cells*) (Suzuki 2003). Aggressive forms of Krabbe disease, such as the early infantile form, are associated with extensive central and peripheral effects including brain atrophy, spasticity, loss of hearing and vision, seizures, weight loss, aspiration, loss of development milestones and early mortality.

Study objective

This first-in-human study is planned to include both a dose ranging phase and a confirmatory phase, with the intention that all data collected throughout the study may support registration. The dose ranging phase will be conducted in cohorts of 3-4 subjects with early infantile Krabbe disease in which the assessment of safety will be the primary objective. Doses selected for administration in the dose ranging phase are expected to be safe and have the potential to confer therapeutic benefit to study subjects as determined from the nonclinical development program. If the safety and biomarker data from the dose ranging phase supports progression to the confirmatory phase of the study, the primary objectives for the confirmatory component will include both safety and efficacy.

Study design

Overview of Study Design:
Pediatric subjects aged >=1 to <9 months (maximum of 28 subjects) with early infantile Krabbe disease, either presymptomatic or symptomatic with onset of symptoms at <=6 months of age, will be enrolled.

All subjects will receive a single dose of PBKR03 administered by ICM injection and will be assessed for 2 years for safety, tolerability and efficacy, and then for an additional 3 years of follow-up for safety and durability of effect. Starting 1 day prior to PBKR03 administration, systemic corticosteroids will be administered for approximately 1 month, and then the corticosteroid dose will be tapered gradually over approximately 1 month until normal adrenal function has been documented. Subjects may be followed beyond 5 years in accordance with local regulations.

The dose ranging portion of this study will enroll independent dose escalation cohorts in 2 age groups of subjects with early infantile Krabbe disease, for a planned total of 12 subjects in 4 cohorts:
• Cohort 1: 3 subjects aged >=4 to <9 months will receive the low dose (Dose I)

• Cohort 2: 3 subjects aged >=4 to <9 months will receive the high dose (Dose II)
• Cohort 3: 3 subjects aged >=1 to <4 months will receive the low dose (Dose I)
• Cohort 4: 3 subjects aged >=1 to <4 months will receive the high dose (Dose II)

Due to limited clinical experience with the ICM procedure in children, this study will initially enroll subjects aged >=4 months. Three subjects will be enrolled into the low dose cohort (Cohort 1, Dose I) prior to consideration of dose escalation. Safety will be monitored by the Sponsor and an Independent Data Monitoring Committee (IDMC), and ongoing safety management of subjects will be based on adverse events (AEs) and stopping rules prospectively defined in this protocol. After safety and pharmacodynamic (PD) data are reviewed from all subjects in Cohort 1 and determined to be acceptable by the IDMC, the study may proceed to enroll additional subjects of the same age group into the high dose cohort (Cohort 2, Dose II). Also, at that time, subjects aged <4 months and as young as 1 month of age can then be enrolled in the low dose cohort (Cohort 3, Dose I). Enrollment of subjects aged <4 months and as young as 1 month of age into the high dose cohort (Cohort 4, Dose II) will proceed if criteria outlined above are met.
If a treatment-related PD response (i.e., change in levels of GALC activity or psychosine) is not certain because of variability of the response in the first 3 subjects dosed in Cohort 1 or Cohort 3, an additional subject may be enrolled at the same dose level before dose escalation. If a treatment-related moderate AE (Common Terminology Criteria for Adverse Events [CTCAE] Grade 2) occurs in 1 of the first 3 subjects dosed in a cohort, an additional subject will be enrolled in the same dose cohort.
Occurrence of certain AEs that are prospectively defined in this protocol suggests that the Maximum Tolerated Dose (MTD) may have been reached or exceeded, and further dosing will not continue until the IDMC is convened to review all available data, determine whether the MTD was reached, and made a recommendation whether the study should continue in its original design, continue with modification (e.g, dose de-escalation), or cease enrollment.
Review of all available data from one of the low dose cohorts may also lead the IDMC to recommend escalation to a dose that is lower than the one originally planned (e.g., smaller incremental increase). During the ongoing dose ranging phase of the study the IDMC will review data pooled from both low dose cohorts (Cohort 1 and Cohort 3) or from both high dose cohorts (Cohort 2 and Cohort 4) to assess the effects of Dose I and Dose II and help inform recommendations on study conduct.
Enrollment of individual subjects within a cohort will be separated by a minimum of 60 days to allow assessment of 30-day biomarker and nerve conduction study (NCS) data and 60-day safety data.
The dose ranging cohorts are intended to define a dose for further evaluation in an expanded, confirmatory cohort. The optimal dose for the confirmatory cohort (which will not exceed the doses tested in the dose escalation cohorts) will be chosen based on available safety, tolerability, biomarker, and clinical data collected in the dose ranging cohorts. This optimal dose will be further characterized in the confirmatory cohort, in which 12 subjects are expected to

be enrolled. All subjects in the confirmatory cohorts may be enrolled simultaneously. It is anticipated that an integrated analysis of pooled data from all cohorts will be sufficient to make conclusions regarding the safety and efficacy of PBKR03 in this rare disease.

Intervention

In order to more effectively deliver GALC to cells throughout the CNS while minimizing procedure-related morbidity, AAV vector delivery into the CSF has been evaluated.

PBKR03 to be administered by ICM injection

Study burden and risks

In summary, when comparing the risks of PBKR03 administration, additional risk of procedures that may be invasive or require anesthesia/sedation such as MRIs, LPs, or nerve conduction testing versus the devastating clinical course of early infantile Krabbe disease, the anticipated benefit of correcting the underlying pathophysiology and improving developmental potential and survival outweigh the potential risks associated with PBKR03 and study procedures all listed in the protocol chapter 5.3.2

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. >= 1 month and <9 months of age at enrollment, and are presymptomatic or symptomatic with first symptoms of Krabbe disease at <=6 months of age
2. Leukocyte GALC activity <=lower limit of normal (LLN)
3. Whole blood (dried blood spot) psychosine > 10 nM
4. Biallelic pathogenic GALC gene variants associated with early infantile Krabbe disease or variants classified as likely pathogenic (testing must be done at a Clinical Laboratory Improvement Amendments [CLIA] or CLIA-equivalent laboratory certified per local standard. If the GALC gene analysis is performed in the UK or the European Union (EU) a Conformité Européenne (CE) marked test will be used). See also Appendix 2 of Protocol, Classification of GALC Gene Variants.
Note: Subjects without documentation of two pathogenic or likely pathogenic GALC variants but who meet all other inclusion criteria, including low GALC activity and high psychosine level, may be considered eligible for the study. In this case the totality of available data, including relevant family history, must be consistent with a diagnosis of early infantile Krabbe disease. For the full list of inclusion criteria see chapter 6.1 of the protocol

Exclusion criteria

1. Any clinically significant neurocognitive deficit not attributable to Krabbe disease
2. An acute illness requiring hospitalization within 30 days of enrollment that in the opinion of the investigator would interfere with the evaluation of the investigational product or interpretation of subject safety or study results.
3. History of chronic ventilation assisted respiratory support (defined as use of more than 12 hours/day of bilevel positive airway pressure, continuous positive airway pressure, or ventilator) or a need for tracheostomy as a result of their disease. Note: This does not exclude subjects who use respiratory vests.
4. Intractable seizure or uncontrolled epilepsy defined as having had an episode of status epilepticus, or seizures requiring hospitalization.

a. This does not exclude subjects who have a history of staring spells that have not been associated with EEG findings
5. Family history of seizure disorders or epilepsy of infantile or childhood onset, other than febrile seizures
a. This does not exclude subjects with a family history of Krabbe disease
6. Any contraindication to ICM administration procedure, including contraindications to fluoroscopic imaging, IT contrast and anesthesia, or any condition that would increase the risk of adverse outcomes from the ICM procedure, including but not limited to the presence of space occupying lesion causing mass effect or signs of increased intracranial pressure, non-communicating hydrocephalus, space-occupying lesion in the posterior fossa or foramen magnum, aberrant vascular anatomy such as a large midline posterior inferior cerebellar artery, venous anomaly such as a large midline cerebellar vein or occipital sinus, congenital anatomical abnormalities such as Chiari malformation.For the full list of exclusion criteria see chapter 6.2 of the protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	28-06-2021
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	11-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-08-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005229-95-NL
CCMO	NL76430.000.21