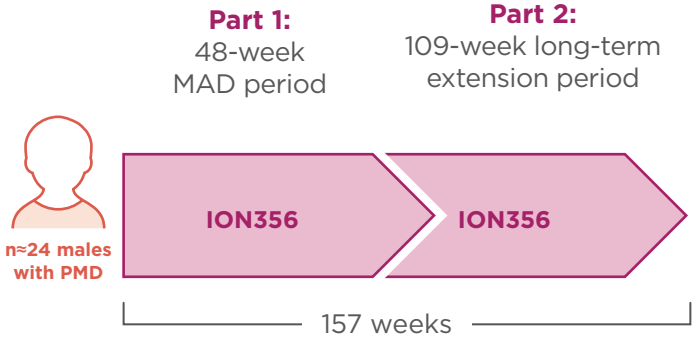
Orbit Study: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Intrathecally Administered ION356 in Patients With Pelizaeus-Merzbacher Disease (PMD)[1]

Study objective:

To evaluate the safety and tolerability of an investigational RNA-targeted medicine (RTM), ION356, in patients with PMD and *PLP1* duplication. This study will evaluate pharmacokinetics (PK), biomarkers, and outcomes relevant to PMD.[1,2]



This is a multicenter, multiple-ascending dose (MAD), multipart study of ION356. **Part 1** is the MAD treatment period in which patients will receive ION356 at multiple ascending dosages for 48 weeks. This is followed by **Part 2**, a 109-week long-term extension period. Multiple dosing cohorts will be evaluated in the study.[1,2]

Select inclusion/exclusion criteria[1]:

- Diagnosis of PMD with genetic confirmation of *PLP1* gene duplication[a]
- Clinical phenotype and brain imaging consistent with a diagnosis of PMD
- Male aged 2-17 years[b]
- Patients with clinically significant abnormalities rendering them unsuitable for participation are excluded[c]

For more study information, scan here:

Table: Key Clinical Endpoints[1,2,d]

Primary Endpoints	Incidence of treatment-emergent adverse events and serious treatment-emergent adverse events from Day 1 to final study visit Change from baseline over the course of the study in: • Laboratory assessments • Neurological exam and vital signs • Electrocardiography • Concomitant medication use
Secondary Endpoints	Characterization of the CSF and plasma PK of ascending dose levels of multiple intrathecal administrations of ION356

ION356 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

[a]Patients with >2 copies of *PLP1* are excluded.[1] [b]Patients can have a trial partner (parent, caregiver, or other).[1] [c]Abnormalities include, but are not limited to, obstructive hydrocephalus and known brain or spinal disease or previous spinal surgery that would interfere with the lumbar puncture process, CSF circulation, or safety assessment.[1] [d]List is non-comprehensive.
CSF, cerebrospinal fluid; *PLP1*, proteolipid protein 1.
1. ClinicalTrials.gov. Accessed February 1, 2024. https://clinicaltrials.gov/ct2/show/NCT06150716/ 2. Ionis Pharmaceuticals. Data on file.

ION356 Is an Investigational RNA-Targeted Medicine (RTM) That Has Been Designed to Reduce CNS Expression of PLP1[1-4]

Proposed ION356-Mediated Downregulation of *PLP1*[1-4]

ION356 is administered directly to the CNS via lumbar intrathecal bolus injection[4]

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For more information or questions about participating sites, please contact us at **IonisPelizaeusMerzbacherStudy2@clinicaltrialmedia.com** or **(844) 387-9520.**[4]

CNS, central nervous system; dsDNA, double-stranded DNA; mRNA, messenger RNA; PLP1, proteolipid protein 1.

1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 2. Dhuri K, et al. *J Clin Med*. 2020;9(6):2004. 3. Ionis Pharmaceuticals. Data on file. 4. ClinicalTrials.gov. Accessed February 1, 2024. https://clinicaltrials.gov/ct2/show/NCT06150716/