Phase 1-3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ION373 in Patients with Alexander Disease

Published: 09-02-2021
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This study has been transitioned to CTIS with ID 2024-510603-11-00 check the CTIS register for the current data. Primary Objective: To evaluate the efficacy of ION373 in improving or stabilizing gross motor function in patients with Alexander...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON54391

Source
ToetsingOnline

Brief title
Alexander Disease

Condition

- Congenital and hereditary disorders NEC

Synonym
AxD, neurodegenerative disease

Research involving

Human

Sponsors and support

Primary sponsor: Ionis Pharmaceuticals
Source(s) of monetary or material Support: the sponsor;Ionis Pharmaceuticals.

Intervention

Keyword: Alexander disease, ION373, Phase 1-3, Placebo-controlled

Outcome measures

Primary outcome

Percent change from Baseline to Week 61 in the 10MWT in patients who are in

Stratum 1.

Secondary outcome

Key Secondary Endpoints:

Change from Baseline to Week 61 or value at Week 61 for the following:

• Patients* self-identified most bothersome symptom (based on a Likert scale

for change; all patients)

• PedsQL Generic Core Scales (all patients)

• Patient Global Impression of Severity (PGIS; all patients)

• Patient Global Impression of Change (PGIC; all patients)

• Clinical Global Impression of Change (CGIC; all patients)

Other Secondary Endpoints:

Change from Baseline to Week 61 or value at Week 61 for the following:

• Gross Motor Function Measure-88, Dimensions C, D and E (GMFM 88, Dimensions

C-E; patients < 5 years old at Screening) or 10MWT (patients >= 5 years old at

Screening)

• 9-Hole Peg Test (9HPT; patients >= 8 years old at Screening)

• Vineland-3 Motor Skills Domain (patients < 8 years old at Screening)

• PedsQL Gastrointestinal Symptoms Scales (all patients)

• Vineland-3 Adaptive Behavior Composite (ABC) Score (patients < 18 years old at Screening)

• Composite Autonomic Symptom Score 31 (COMPASS-31; patients >= 18 years old at Screening)

• CSF GFAP levels (all patients)

• Clinical Global Impression of Severity (CGIS; all patients)

• Alexander Disease Patient Domain Impression of Severity (AxD PDIS; all patients)

• Alexander Disease Patient Domain Impression of Change (AxD-PDIC; all patients)

• Body weight percentile (for patients < 18 years old at Screening) or body weight (for patients >= 18 years old at Screening

Study description

Background summary

Alexander disease is a disease caused by a small error in your GFAP gene, which is the region in the DNA (genetic material, deoxyribonucleic acid: the characteristics that expresses the color of hair or eyes, *) that contains the instructions for the production of a protein with the same name (GFAP). This small error in the genetic instructions leads to overproduction of GFAP in the brain. The excess GFAP forms protein clumps known as Rosenthal fibers that cause cell malfunction and death. This is thought to cause the destruction of the fatty covering that surrounds and protects the nerve fibers (the myelin

sheath). Destruction of the myelin sheath leads to the symptoms associated with Alexander disease. The intended effect of ION373 is to reduce GFAP levels, thereby avoiding further destruction of the myelin sheath and potentially altering the course of disease.
This ongoing clinical research study is the first time ION373 has been tested in humans. As the study is still ongoing, it is not yet known whether or not ION373 is safe or effective in humans. There are currently no commercially available drugs that treat the underlying cause(s) of Alexander disease.

Study objective

This study has been transitioned to CTIS with ID 2024-510603-11-00 check the CTIS register for the current data.

Primary Objective: To evaluate the efficacy of ION373 in improving or stabilizing gross motor function in patients with Alexander disease
Secondary Objectives: To further evaluate the efficacy of ION373 in improving or stabilizing disease manifestations across the full range of affected domains (gross and fine motor, communication, swallowing, autonomic and/or other gastrointestinal functions, nutritional/growth status) in patients with Alexander disease

Study design

This is a registration supporting (Phase 1-3), double-blind, randomized, placebo-controlled study conducted at multiple centers. This study is composed of 4 periods - a 60-week Double-Blind Treatment Period; a 60-week Open Label Treatment Period; a 120-week open-label, long-term extension (LTE); and a 28-week Post-Treatment Follow-Up Period.
Study Drug is administered at 12-week intervals. Up to 3 different dose cohorts (A, B and C) may be included in the study:
Cohort A: 25 mg ION373 or placebo (2:1) intrathecal bolus (ITB) injection
Cohort B: 50 mg ION373 or placebo (2:1) ITB injection
Cohort C (optional): up to 75 mg ION373 or placebo (2:1) ITB injection
Interim safety and PK data collected in Cohorts A and B will be reviewed to determine if evaluation of an additional dose level is warranted. If warranted, 1 additional cohort (Cohort C) will be enrolled.
Under a sentinel dosing strategy, in each dose-level cohort, 1 of the first 2 patients will be assigned to ION373 and the other will be assigned to placebo. No additional patients will initiate dosing in the cohort until at least 7 days after completion of the first dose in these first 2 patients.
In each dose-level cohort, the first 6 patients enrolled (i.e., the 2 sentinel patients and the next 4 patients) must be at least 8 years of age at the time of Screening. No additional patients will initiate dosing in the cohort until at least 7 days after completion of the first dose in these first 6 patients.
During the Double-Blind Treatment Period, a blinded rescue plan will be

implemented. Patients will be assigned to ION373 beginning with the dose at Week 49 if they:
• Have experienced a clinical decline that corresponds to a score of 2 on at least 1 of the clinical outcome assessments (COAs) in the most bothersome symptom endpoint (3 domains: gross motor, gastrointestinal and cognitive) at Week 37, and a score -1 or -2 on the same COA at Week 25, and
• Have a reduction in CSF glial fibrillary acid protein (GFAP) levels < 25% (compared to Baseline) at Week 37
The CSF GFAP data generated for consideration of rescue will not be shared with the blinded study team, and implementation of the rescue plan will be blinded.
This study includes an open-label sub-study in patients < 2 years of age. Patients included in the sub-study will be enrolled in Cohort D. and participate in 3 periods * a 60-week Open-Label Treatment Period; a 120-week, open-label, long-term extension (LTE); and a 28-week Post-Treatment Follow-Up Period.
Patients who discontinue treatment during the Double-Blind or Open-Label Treatment Period early or whose treatment assignment was unblinded due to a safety issue will not be allowed to participate in the LTE and, instead, will proceed directly to the Post-Treatment Follow-Up Period. Dose levels and dosing regimen in the LTE could be based on ongoing review of safety, PK/PD profile by the Data Safety Monitoring Board (DSMB) and the Sponsor. Patients who prematurely discontinue from treatment will be encouraged to complete the Post-Treatment Follow-Up Period.

Intervention

This study has four parts, and all participants will participate in parts 1 and 2 of the study:

Double-blind treatment period (Part 1):
Part 1 of the study is double-blind and placebo-controlled which means the patient will be randomly assigned (like drawing numbers out of a hat) to receive ION373 or the placebo (a solution made to look like the ION373, but contains no medicine). The patient has approximately a 67% chance of being assigned to ION373 and approximately a 33% chance of being assigned to the placebo. The patient will also be placed in 1 of 3 groups (Group A, B, or C) based on when you are enrolled in the study. Neither the patient nor the study staff will know whether the patient has been assigned to receive ION373 or placebo, that*s why this is called a double-blind trial. In case of an emergency, the study staff can get this information. In Part 1 of this study the patient will receive 5 doses of study drug (either ION373 or placebo) every 12 weeks over a 60-week period.
o If the patient is randomly assigned to ION373, the patient will receive ION373 for all 5 doses.
o If the patient is randomly assigned to placebo, the patient will receive placebo for all 5 doses or for 4 doses of placebo and 1 dose of ION373.
Neither the patient nor the study staff will know whether the patient received

5 or 4 doses of placebo.

The patient will be returning to the hospital a total of 13 times during this period for clinical assessments, physical exams, ECGs, blood tests, and study drug administrations. Injection visits will be approximately 8-24 hours long (spanning across two days). Non-injection visits will be approximately 2 to 4 hours long. The patient will also receive 15 follow up phone calls from the study staff to ask about changes in medications and to ask whether or not the patient has experienced any side effects.

Open label treatment period (Part 2):
Part 2 of the study is open label, which means that all patients will receive ION373. In Part 2 of the study, the patient will receive the dose associated within the patients' assigned group or they will receive the highest dose of ION373 that has been tested and determined to be well tolerated. During Part 2, the patient will receive 5 doses of ION373 every 12 weeks over a 60-week period.

The patient will be returning to the hospital a total of 11 times for clinical assessments, physical exams, ECGs, blood tests, and ION373 administrations. Injection visits will be approximately 8-24 hours long (spanning across two days). Non-injection visits will be approximately 2 to 4 hours long , except for the non-injection visit that requires a brain scan and several other clinical assessments which will be approximately 6-7 hours long dependent on scheduling and other assessments required. The patient will also receive 16 follow up phone calls from the study staff to ask about changes in medications and to ask whether or not you have experienced any side effects.

Long-Term Extension (Part 3):
Part 3 of the study is the long-term extension. This means that patients from Group A, B, and C will receive the ION373 dose associated with their dose in the Open-Label part or the highest dose that has been tested and determined to be well tolerated, whichever is higher. They will receive 10 doses of ION373 every 12 weeks over a 120-week period.

The patients will be returning to the hospital a total of 10 times for neurological and physical examinations and examination of their vital signs. These tests may include clinical laboratory tests and ION373 administrations. Injection visits will be approximately 8-24 hours long (and may span across two days). The patients will also receive 20 follow- up phone calls from the study staff to ask about changes in medications and to ask whether or not they have experienced any side effects.

Post treatment follow- up period (Part 4):
Part 4 of the study is post-treatment follow-up period in which no drug will be given to the patients. This period is 28 weeks, and all patients will be encouraged to complete the post-treatment follow-up period, even patients who

prematurely discontinue from treatment.

The patients will return to the hospital a total of two times for study assessments.

Study burden and risks

See the Schedule of Events, in Appendix A of the protocol (pages 81-85) for a detailed overview of the visits, procedures and tests.

The risks related to participation in this research are described in the Informed Consent Form, Chapter 6.

Contacts

Public
Ionis Pharmaceuticals

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Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

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

Inclusion criteria

1. Clinical phenotype and brain imaging consistent with a diagnosis of Alexander disease
2. Documented genetic mutation in the GFAP gene
3. Aged >= 2 to 65 years old at the time of informed consent (eligibility for main study) or aged < 2 years old at the time informed consent was obtained (eligibility for the open-label sub-study)
4. Able and willing to meet all study requirements (in the opinion of the Investigator), including travel to Study Center, procedures, measurements and visits
5. Patients < 18 years old at Screening must have a trial partner (parent, caregiver or other) who is reliable, competent and at least 18 years of age, is willing to accompany the patient to the trial visits and to be available to the Study Center by phone if needed, and who (in the opinion of the Investigator) is and will remain sufficiently knowledgeable of patient's ongoing condition to respond to Study Center inquiries about the patient
6. If aged >= 2 and < 5 years old, must be able to sit with minimal assistance (using only own hands for support) for at least 10 seconds, or must be ambulatory (defined as able to complete the 10-meter walk test (10MWT) in 5 minutes or less [assistive walking devices such as braces, canes, walkers permitted]); if aged >= 5 years old, must be ambulatory
7. Stable medications, nutritional support and physical, occupational and, speech, and respiratory therapy for at least 3 months prior to Screening

Exclusion criteria

1. Clinically significant abnormalities in medical history or physical examination
2. Platelet count or any other clinically significant laboratory abnormalities that would render a patient unsuitable for inclusion
3. Any contraindication or unwillingness to undergo MRI
4. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer; concurrent participation in any other clinical study (including observational and non-interventional studies)
5. Previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received or history of hypersensitivity to ION373 or its excipients or history of hypersensitivity to any ASO. This exclusion does not apply to vaccines (both mRNA and viral vector

vaccines).
6. History of gene therapy or cell transplantation or any other experimental brain surgery
7. Current obstructive hydrocephalus
8. Presence of a functional ventriculoperitoneal shunt for the drainage of CSF or an implanted CNS catheter
9. known brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment.
10. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks prior to Screening or planned during the study
11. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
12. History of gene therapy or cell transplantation or any other experimental brain surgery
13. Current obstructive hydrocephalus
14. Presence of a functional ventriculoperitoneal shunt for the drainage of CSF or an implanted central nervous system (CNS) catheter
15. Any condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
16. Known brain or spinal disease that would interfere with the lumbar puncture (LP) process, CSF circulation or safety assessment, including tumors or abnormalities by MRI or computed tomography, subarachnoid hemorrhage, spinal stenosis or curvature, Chiari malformation, syringomyelia, tethered spinal cord syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome
17. History of severe post-LP headache and/or blood patch
18. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks prior to Screening or planned during the study
19. Recent history of, or current drug or alcohol abuse
20. Antiplatelet or anticoagulant therapy within the 14 days prior to Screening or anticipated use during the study, including but not limited to aspirin (unless <= 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban
21. 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, such as the presence of a chronic condition which places the patient at higher risk from procedural sedation or anesthesia if this is deemed necessary by the Investigator for completion study procedures including the lumbar punctures and/or brain MRI scans

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-09-2021
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	09-02-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	29-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	27-10-2023
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
EU-CTR	CTIS2024-510603-11-00
EudraCT	EUCTR2020-000976-40-NL
CCMO	NL75028.000.21