A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

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Primary objective:To evaluate the efficacy of ION-682884, based on the change from Baseline in serum Transthyretin (TTR) concentration, modified Neuropathy Impairment Score +7 (mNIS+7), and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON55279

Source
ToetsingOnline

Brief title
NEURO-TTRANSFORM

Condition

- Peripheral neuropathies

Synonym
Familial amyloid polyneuropathy - Transthyretin (TTR) amyloid polyneuropathy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Hereditary Transthyretin-Mediated Amyloid Polyneuropathy, ION-682884

Outcome measures

Primary outcome

Week 35 Interim Analysis: Change from Baseline in serum TTR concentration and

the mNIS+7;

Week 66 Final Analysis: Change from Baseline in serum TTR concentration,

mNIS+7 and Norfolk QOL-DN

Secondary outcome

Secondary endpoints:

Week 35 Interim Analysis:

* Change from Baseline in Norfolk QOL-DN

Week 66 Final Analysis:

* Change from Baseline in the NSC score at Weeks 35 and 66

* Change from Baseline in the PCS score of SF-36 at Week 65

* Change from Baseline in PND score at Week 65

* Change from Baseline in mBMI at Week 65

Additional/Exploratory endpoints:

Change from Baseline in mNIS+7 at Week 85

Change from Baseline in Norfolk QOL-DN at Week 85

Change from Baseline in 10MWT at Weeks 37 and 81

Change from Baseline in R-ODS at Weeks 37 and 81

Change from Baseline in COMPASS-31 at Weeks 37 and 81

Change from Baseline in EQ-5D-5L at Weeks 37 and 81

Change from Baseline in the SF-36 at Week 35

Frequency of all cause hospitalizations in all patients by Week 66

Frequency of all cause hospitalizations in patients with cardiac involvement by Week 66

Change from Baseline in ECHO parameters, including LV mass, LV wall thickness, IVS thickness, and GLS, at Week 65 in patients with cardiac involvement

Change from Baseline in NT-proBNP at Week 65 in patients with cardiac involvement

Change from Baseline in PGIS at Weeks 37 and 85

PGIC at Weeks 37 and 85

Plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, area under the curve (AUC), Cmax, and tmax in a subset of patients, and t**z for patients who do not roll over to the OLE study.

Safety endpoints:

Change from Baseline in platelet count per Common Terminology Criteria for Adverse Events (CTCAE) grade.

Change from Baseline in renal function.

Additional safety endpoints include: adverse events, vital signs and weight, physical examination, clinical laboratory tests, ECG, use of concomitant

medication, ophthalmology examination, thyroid panel, inflammatory panel,

coagulation, and immunogenicity

Study description

Background summary

See section 2 of the enclosed protocol

Study objective

Primary objective:
To evaluate the efficacy of ION-682884, based on the change from Baseline in serum Transthyretin (TTR) concentration, modified Neuropathy Impairment Score +7 (mNIS+7), and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) as compared to the historical control of placebo arm in the ISIS 420915-CS2 NEURO-TTR (inotersen) trial

Secondary objectives:
To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in:
* Neuropathy Symptom and Change (NCS) score
* Physical Component Summary (PCS) score of 36-Item Short Form Survey (SF-36)
* Polyneuropathy disability (PND) score
* Modified body mass index (mBMI)

Additional/Exploratory objectives:
To evaluate the efficacy of ION-682884 in mNIS+7 at Week 85, compared to Baseline.
To evaluate the efficacy of ION-682884 in the Change from Baseline in the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at Weeks 37 and 85.
To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm in the ALN-TTR02-004 trial (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) in:
* Change from Baseline in Norfolk QOL-DN at Week 85
* Change from Baseline in 10-Meter Walk Test (10MWT)
* Change from Baseline in Rasch-built Overall Disability Score (R ODS)
* Change from Baseline in Composite Autonomic Symptom Score-31 (COMPASS-31)
* Change from Baseline in 5 Level EQ-5D (EQ-5D-5L)
To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, in:
* Change from Baseline in the SF-36

* Frequency of all-cause hospitalizations (in all patients and in patients with cardiac involvement)
* Change from Baseline in transthoracic echocardiogram (ECHO) parameters including left ventricular (LV) mass, LV wall thickness, intraventricular septum (IVS) thickness, global longitudinal strain (GLS), in patients with cardiac involvement
* Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with cardiac involvement
To evaluate the plasma trough and post-treatment concentrations of ION 682884 or inotersen in all patients, and to evaluate plasma pharmacokinetic (PK) parameters in a subset of patients.

Safety objectives:
To evaluate safety and tolerability of ION-682884 in hATTR-PN patients, in the following measures: change from Baseline in platelet count and renal function, adverse events, vital signs and weight, physical examination findings, clinical laboratory tests, electrocardiogram (ECG) parameters, use of concomitant medication, ophthalmology examination, thyroid panel tests, inflammatory panel tests, coagulation tests, and immunogenicity tests.

Study design

This is a multicenter, open-label study with historical controls and an active reference arm (inotersen). Approximately 140 patients will be randomized 6:1 to receive subcutaneous (SC) injections of either ION-682884 (n = 120) once every 4 weeks or inotersen (n = 20) once a week. Patients will also take daily supplemental doses of the recommended daily allowance of vitamin A.
An interim analysis will be conducted at Week 35. Primary endpoint (PEP) analysis will be performed at Week 66.
Patients included in the inotersen reference arm will be crossed over to ION-682884 at Week 37 after completing the Week 35 assessments.
All patients will continue dosing with ION-682884 until Week 81 with end of-treatment (EOT) assessments at Week 85, 4 weeks after the last dose.
At Week 35, an interim analysis will be performed in hierarchical order for the following 3 efficacy endpoints: 1) serum TTR reduction; 2) mNIS+7; 3) Norfolk QOL-DN.
At Week 66, co-primary endpoints will be: 1) serum TTR reduction; 2) mNIS+7; 3) Norfolk QOL-DN.
Following treatment and the EOT assessments, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the appropriate regulatory authorities. All participating patients in the OLE study will continue to receive ION-682884 once every 4 weeks. Patients not participating in the OLE will enter the 20-week post treatment evaluation portion of this study after completing the EOT assessments.
A Data and Safety Monitoring Board (DSMB) will be established to review safety, tolerability and efficacy data (as needed) collected during this study, both

individual events and aggregate data.

Intervention

Please refer to section E6 of the protocol.

Study burden and risks

Inotersen was administered to over 100 patients with polyneuropathy in a medical-scientific trial comparing to placebo. The most common side effects (may affect more than 20% of people) of inotersen treatment were:
* Injection site reactions (may include pain, redness, swelling, itching, rash, bruising, and change in color at the injection site)
* Nausea and/or vomiting
* Headache
* Tiredness
* Low amount of platelet in the blood
* Diarrhea and/or constipation
* Feeling faint or dizzy, especially on standing up (low blood pressure, hypotension)
* Fever

Serious side effects of inotersen and how this may relate to ION-682884
Severely reduced platelet count (<3% patients taking inotersen)
Low platelet count is a common side effect of inotersen (occurring in <3% of patients in the study).
ION-682884 is very similar drug to inotersen although at much lower dose, reduction of platelets is therefore considered a potential risk for ION-682884.

Kidney inflammation (glomerulonephritis) (<3% in patients taking inotersen)
Both kidney inflammation and a decrease in kidney function have been observed in patients taking inotersen in a medical-scientific trial. In one of these patients, the kidney inflammation led to the need for dialysis.
ION-682884 and inotersen are similar to each other and are known to accumulate in the kidney. Side effects of the kidney have not been observed in the ongoing healthy volunteer study with ION-682884. ION-682884 has not yet been tested in polyneuropathy patients. Thus, kidney side effects are considered as a potential risk for ION-682884.

Full list of risks can be found in the enclosed informed consent form

Patient's participation in this study may involve known or unknown risks for pregnant women, unborn children, or breastfed babies. This is why pregnant or breastfeeding women may not participate in this study and every effort to avoid pregnancy is important during the participation in this study

Because the study drug may be transferred in seminal fluid, every effort to avoid pregnancy is important for partners of male patients. In addition, males must either be abstinent which means they will not have sexual relations with a woman who is already pregnant or able to get pregnant or use a highly effective contraceptive method during the study and for at least 24 weeks after taking the last dose of study drug. Male patients whose female partner becomes pregnant or is pregnant must use a condom to protect the fetus.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements

2. Aged 18 to 82 years at the time of informed consent
3. Satisfy the following:
a. Females: must be non-pregnant and non-lactating and either:
i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females * 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved)
iii. Abstinent* or
iv. If engaged in sexual relations of child-bearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION*682884 or inotersen and agree to receive a monthly pregnancy test
b. Males: Surgically sterile (i.e., bilateral orchidectomy) or, if engaged in sexual relations with a woman of child bearing potential (WOCBP), the patient or the patient*s non-pregnant female partner must use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION*682884 or inotersen.
* Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.
4. hATTR-PN as defined by meeting all 3 of the following criteria:
a. Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy (FAP) or Coutinho Stage
b. Documented genetic mutation in the TTR gene
c. Symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including NIS * 10 and * 130
5. Willingness to adhere to vitamin A supplementation per protocol

Exclusion criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
a. Urine protein/creatinine ratio (UPCR) * 1000 mg/g. In the event of UPCR above this threshold, eligibility may be confirmed by a repeat random urine

test with UPCR < 1000 mg/g or a quantitative total urine protein measurement of < 1000 mg/24 hr
b. Renal insufficiency as defined by estimated glomerular filtration rate (eGFRcreat-cys) < 45 mL/min/1.73 m2 at Screening (eGFRcreat-cys is calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine-cystatin C equation from 2012) (Inker et al. 2012)
c. Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may be confirmed with urine microscopy showing * 5 red blood cells per high power field
d. Alanine aminotransferase/ aspartate aminotransferase (ALT/AST) > 2 × upper limit of normal (ULN)
e. Bilirubin * 1.5 × ULN (patients with bilirubin * 1.5 × ULN may be allowed on study if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert*s disease)
f. Platelets < 125 × 109/L
g. HbA1C * 7%
h. Abnormal thyroid function tests with clinical significance per Investigator judgement in consultation with the Sponsor Medical Monitor
i. Serum vitamin A (or retinol) level at Screening < lower limit of normal (LLN). For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and vitamin A < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as dry eye, Bitots* spot observed in the ophthalmology exam, that in the opinion of the ophthalmologist is consistent with vitamin A deficiency)
1. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
2. Unwillingness to comply with study procedures, including follow up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
3. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C (patients confirmed as cured from previous hepatitis C can be included) or chronic hepatitis B
4. Uncontrolled hypertension (BP > 160/100 mm Hg)
5. 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
6. Current treatment with any approved drug for hereditary TTR amyloidosis such as Vyndaqel® / Vyndamax* (tafamidis), Tegsedi* (inotersen), Onpattro* (patisiran), off-label use of diflunisal, doxycycline or tauroursodeoxycholic acid (TUDCA). If previously treated with Vyndaqel® / Vyndamax*, diflunisal or doxycycline, and TUDCA, must have discontinued treatment at least 2 weeks prior to Study Day 1
7. Previous treatment with Tegsedi* (inotersen) or Onpattro* (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA)
8. Treatment with another investigational drug, biological agent, or device

within 3 months of screening, or 5 half-lives of study agent, whichever is longer
9. History of bleeding, diathesis or coagulopathy
10. Recent history of, or current drug or alcohol abuse
11. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of ION*682884 or inotersen and regular clinical monitoring is performed
12. Karnofsky performance status * 50%
13. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, diabetic neuropathy)
14. Prior liver transplant or anticipated liver transplant within 1 year of Screening
15. New York Heart Association (NYHA) functional classification of * 3
16. Known immunoglobulin light chain amyloidosis (AL amyloidosis)
17. Known leptomeningeal amyloidosis
18. Known multiple myeloma
19. Monoclonal gammopathy of undetermined significance (MGUS) and/or immunoglobulin free light chain ratio < 0.26 and > 1.65 unless fat, bone marrow, or heart biopsy confirming the absence of light chain by mass spectrometry or immunoelectron microscopy
20. Presence of known type 1 or type 2 diabetes mellitus
21. Anticipated survival less than 2 years
22. 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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Ethics review

Approved WMO Date:	01-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2021
Application type:	First submission
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	EUCTR2019-001698-10-NL
ClinicalTrials.gov	NCT04136184
CCMO	NL73848.000.21