A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Polyneuropathy (ATTRibute-PN Trial)

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Primary:To determine the efficacy of AG10 in the treatment of subjects with symptomatic transthyretin amyloid polyneuropathy (ATTR-PN) by evaluating the difference between the AG10 and placebo groups in Modified Neuropathy Impairment Score + 7 (mNIS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON49272

Source
ToetsingOnline

Brief title
Efficacy and Safety of AG10 in participants with ATTRibute-PN; AG10-333

Condition

- Peripheral neuropathies

Synonym
Transthyretin Amyloid Polyneuropathy (ATTR-PN)

Research involving
Human

Sponsors and support

Primary sponsor: Eidos Therapeutics, Inc.
Source(s) of monetary or material Support: Eidos Therapeutics Inc.

Intervention

Keyword: AG10, Phase 3, Symptomatic Transthyretin Amyloid Polyneuropathy (ATTR-PN)

Outcome measures

Primary outcome

* Change from baseline to Month 18 of treatment in mNIS+7

Secondary outcome

* Change from baseline to Month 18 of treatment in Norfolk QOL-DN, mBMI, and COMPASS-31

* Change from baseline to Month 3 and subsequent visits of treatment in PD endpoints using an established assay of TTR stabilization including Fluorescent Probe Exclusion (FPE) assay

* Change from baseline in prealbumin levels at month 3 and subsequent visits

* Change from baseline to Month 18 of treatment in Dyck/Rankin Score

* Change from baseline to Month 18 of treatment in gait speed (measured as 10-meter walk time)

* Additional assays comparing AG10 activity across a panel of TTR mutations

* Change from baseline in N-terminal pro-Brain-type Natriuretic Peptide (NT-proBNP) and Troponin I (TnI)

* PK measures of AG10 and its predominant metabolite after oral administration BID in subjects with symptomatic ATTR-PN

* Change from baseline to Month 18 of treatment on NSC

* Safety parameters to be assessed: treatment- emergent serious adverse events (SAEs), adverse events (AEs) leading to treatment discontinuation, AEs, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, changes in clinical safety laboratory parameters of potential clinical concern and Columbia-Suicide Severity Rating Scale (C-SSRS).

Study description

Background summary

Our bodies normally have a protein called Transthyretin in our blood. In some patients, due to a genetic mutation, the transthyretin protein becomes unstable and forms misfolded clumps called amyloid, which then deposit in our organs and interfere with normal organ function. Symptomatic Transthyretin Amyloid Polyneuropathy (ATTR-PN) occurs when amyloid deposits in nerves and interferes with their normal function. AG10 is a stabilizer that functions by stabilizing the transthyretin protein and preventing it from forming amyloid clumps. AG10 was previously tested in animals, in healthy volunteers and in patients with transthyretin cardiomyopathy. Doctors cannot prescribe AG10 yet (outside a study), because it is not yet approved in the Netherlands for treating patients with ATTR-PN.

Study objective

Primary:
To determine the efficacy of AG10 in the treatment of subjects with symptomatic transthyretin amyloid polyneuropathy (ATTR-PN) by evaluating the difference between the AG10 and placebo groups in Modified Neuropathy Impairment Score + 7 (mNIS+7) at 18 months of treatment relative to baseline

Key secondary:
* To evaluate the effects of AG10 on:
Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN), modified body mass index (mBMI), and Composite Autonomic Score (COMPASS-31) in subjects with symptomatic ATTR-PN

Other secondary:
* To describe the pharmacodynamic (PD) properties of AG10 as assessed by serial

measurements of an established assay of transthyretin (TTR) stabilization
* To assess the pharmacodynamic effects of AG10 as assessed by circulating prealbumin (TTR) concentration as an in vivo biomarker of stabilization
* To evaluate the effect of AG10 on health-related quality of life (QOL) and clinical outcome score as assessed by the Dyck/Rankin Score
* To assess the effect of AG10 on gait speed as a reflection of functional ability

Exploratory:
* To assess the ability of AG10 to bind and stabilize a diverse array of pathogenic and likely pathogenic variant TTR tetrameric species, representing amino acid substitutions located throughout the sequence of TTR that are responsible for a spectrum of clinical presentations, from sera and/or plasma of subjects with ATTR-PN by ex vivo assays and exploratory assays.
* To evaluate the effects of AG10 on circulating biomarkers of myocardial wall stress and microvascular ischemia in subjects with symptomatic ATTR-PN who may also have cardiac involvement.
* To characterize the pharmacokinetics (PK) of AG10 and its predominant metabolite administered orally twice daily (BID) in subjects with symptomatic ATTR-PN
* To evaluate the effects of AG10 on NSC

Safety:
* To evaluate the safety and tolerability of AG10 administered for 18 months to subjects with symptomatic ATTR-PN

Study design

This prospective, randomized, multicenter, parallel-group study will evaluate the efficacy and safety of AG10 in subjects with symptomatic ATTR-PN compared to placebo, on a background of local standard of care. Screening and randomization will be followed by a total of 18 months of blinded, placebo-controlled treatment.
At the end of 18 months of treatment, efficacy of AG10 will be assessed through analyses of the neurologic impairment (mNIS+7), QOL (Norfolk QOL-DN), nutritional status (mBMI), and autonomic symptoms (COMPASS-31).
Eligible subjects will be randomized in a 2:1 ratio to AG10 800 mg or matching placebo administered orally twice daily (BID). Subjects will be stratified at randomization based on Neuropathy Impairment Score (NIS) (cutoff of <30 points and *30 points) and concomitant use of tafamidis (Vyndaqel®, Pfizer) at its labeled dosage and administration of 20mg/day at Screening.
Information on AEs and concomitant medications will be collected throughout the study. The safety and conduct of the study will be monitored by an independent Data Monitoring Committee (DMC).
All subjects that complete the double-blinded treatment period may be eligible to participate in a separate Open Label Extension study of long-term AG10

treatment.

Intervention

Subjects will be assigned to one of two treatment groups:
- one group will receive 800 mg dose of AG10 (2 x 400 mg AG10 HCl tablets); and
- the second group will receive placebo (2 placebo tablets).
Each group will take their study medicine orally twice a day. Orally means the study medicine is taken by mouth.
The group you are in will be selected at random (like rolling of a dice). You will have a 2 to 1 chance of receiving AG10 versus placebo. This means, you will have a 67% chance of receiving AG10, and a 33% chance of receiving placebo.

Study burden and risks

See ICF section 7.0.

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. Be able to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures;
2. Be male or female *18 to *90 years of age;
3. Have Stage I or II symptoms (polyneuropathy disability [PND] *IIIa) of ATTR-PN and an established diagnosis of ATTR-PN as defined by physical exam findings and/or neurophysiological test findings consistent with the diagnosis of ATTR-PN;
4. Have an NIS of 5 to 130 (inclusive) during screening;
5. Have a nerve conduction studies (NCS) score [sum of the sural sensory nerve action potential (SNAP), tibial compound muscle action potential (CMAP), ulnar SNAP, ulnar CMAP, and peroneal CMAP] of *2 points during screening. NCS is a component of mNIS+7;
6. Have a mutation consistent with ATTR-PN either documented in medical history or confirmed by genotyping obtained at Screening prior to randomization. *No genetic testing is needed for subjects who are recipients of domino liver transplants;
7. Have an anticipated survival of *2 years, in the opinion of the Investigator;
8. Have Karnofsky performance status *60 %;
9. Have serum albumin levels >3.0 g/dL;
10. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception beginning with randomization and continuing for 30 days after the last dose of AG10. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control. Postmenopausal state female subjects must be confirmed with plasma follicle-stimulating hormone (FSH) at Screening.

Exclusion criteria

1. Had a prior liver transplantation or is planning to undergo liver transplantation with a wild-type organ graft as treatment for symptomatic ATTR-PN during the study period. Note: Recipients of a *domino* liver transplant from an ATTR-PN donor who have developed ATTR-PN mediated by their graft are allowed under this protocol, as long as re-transplantation to treat ATTR-PN is not planned during the study period and meets all other eligibility criteria;

2. Has sensorimotor or autonomic neuropathy not related to ATTR-PN; for example, autoimmune disease or monoclonal gammopathy, malignancy, or alcohol abuse;
3. Has Vitamin B-12 levels below the lower limit of normal (LLN);
4. Has clinical evidence of untreated hyper/hypothyroidism;
5. Has leptomeningeal TTR amyloidosis;
6. Has Type 1 diabetes;
7. Has had Type 2 diabetes for *5 years;
8. Has active hepatitis B or C or known human immunodeficiency virus (HIV) infection;
9. Has NYHA heart failure classification >Class II;
10. Had acute coronary syndrome, uncontrolled cardiac arrhythmia, or a stroke within 90 days prior to Screening;
11. Has estimated glomerular filtration rate (eGFR) by Modification of Diet for Renal Disease (MDRD) formula <30 mL/min/1.73 m2 at Screening;
12. Has abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) or total bilirubin >3 × ULN;
13. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of
the skin or carcinoma in situ of the cervix that has been successfully treated;
14. Has known hypersensitivity to Investigational Medicinal Product (IMP) (AG10 or placebo), its metabolites, or formulation excipients;
15. Is currently undergoing treatment for ATTR-PN with patisiran, inotersen, or other gene silencing agents, marketed drug products lacking a label indication for ATTR-PN (e.g., diflunisal, doxycycline), natural products or derivatives used as unproven therapies for ATTR-PN (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol), within 14 days, or 90 days for patisiran and 180 days for inotersen prior to dosing. Prior to screening, tafamidis, if already prescribed to potential subjects as part of their established background therapy, is allowed at the labeled dosage and administration of 20 mg/day for the treatment of ATTR-PN with, in the opinion of the Investigator, evidence of disease progression while on tafamidis treatment;
16. Female subjects who are pregnant or breastfeeding. Breastfeeding females must agree to discontinue nursing before IMP is administered. A negative urine pregnancy test at Screening and on Day 1 prior to randomization are required for female subjects of childbearing potential;
17. In the judgment of the Investigator or Medical Monitor, has any clinically important ongoing medical condition or laboratory abnormality or other condition that might jeopardize the subject*s safety, increase their risk from participation, or interfere with the study;
18. Participation in another investigational drug or investigational device study within 30 days prior to dosing or 5 half-lives of the investigational drug, whichever is longer, with potential residual effects that might confound the results of this study;
19. Has any condition that, in the opinion of the Investigator or Medical

Monitor, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism, or a psychiatric condition.

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:	Recruitment stopped
Start date (anticipated):	28-12-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AG10
Generic name:	3-(3-(3,5-DIMETHYL-1H-PYRAZOL-4-YL)PROPOXY)-4-FLUOROBENZOIC ACID

Ethics review

Approved WMO Date:	19-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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Application type:	First submission
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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	EUCTR2018-004670-10-NL
ClinicalTrials.gov	NCT04418024
CCMO	NL74545.056.20