An Open-Label, Long Term Safety and Efficacy Study of Donidalorsen in the Prophylactic Treatment of Hereditary Angioedema (HAE)

Published: 20-06-2022
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This study has been transitioned to CTIS with ID 2023-509201-77-00 check the CTIS register for the current data. Primary ObjectiveTo evaluate the safety of long-term dosing with donidalorsen in patients with HAE. Secondary ObjectivesTo evaluate the…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53420

Source
ToetsingOnline

Brief title
ISIS 721744-CS7

Condition

- Blood and lymphatic system disorders congenital
- Angioedema and urticaria

Synonym
HAE, Hereditary angioedema

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Donidalorsen, Hereditary angioedema, ISIS 721744, Prekallikrein

Outcome measures

Primary outcome

The primary endpoint is the incidence and severity of treatment-emergent

adverse events (TEAEs)

Secondary outcome

Secondary Endpoints:

All the analyses will be performed on both roll-over (OLE) and non-roll-over

(*Switch*) patients:

• The time-normalized number of Investigator-confirmed HAE attacks (per month)

from Week 1 to Week 53

• The time-normalized number of Investigator-confirmed HAE attacks (per month)

from Week 5 to Week 53

• The percentage of Investigator-confirmed HAE attack-free patients from Week 5

to Week 53

• The time-normalized number of moderate or severe Investigator-confirmed HAE

attacks (per month) from Week 5 to Week 53

• The number of Investigator-confirmed HAE attacks requiring acute therapy from

Week 5 to Week 53

• Angioedema Quality of Life (AE-QoL) questionnaire total score over 53 weeks

Exploratory Endpoints:

The analyses will be performed on both roll-over (OLE) and non-roll-over

(*Switch*) patients as shown below:

All patients:

• The time-normalized number of Investigator-confirmed HAE attacks (per month)

from Week 1 to Week 157

• Angioedema Quality of Life (AE-QoL) questionnaire total score over 157 weeks

• Percentage of total days during the Treatment Period that patients are attack

free

• Percentage of total months during the Treatment Period that patients are

attack free

• Duration in days of the longest attack free interval

• Percent of patients that are attack free for 6 or 12 consecutive months

• Mean/median longest attack free interval

• Rate of HAE attacks that involves the larynx

• Plasma PKK levels over 53 weeks

• Angioedema Control Test (AECT) over 53 weeks

• Hereditary Angioedema Quality of Life (HAE-QoL) questionnaire total score

over 53 weeks

• Treatment Satisfaction Questionnaire for Medication (TSQM-II) score over 53

weeks

• Incidence of ER visits, all cause hospitalization and total inpatient days

over 53 weeks

• PK exposure over time and potential exposure-response analysis using relevant

exposure parameters and biomarkers

Open-Label Extension patients only:

• The time-normalized number of Investigator-confirmed HAE attack rate (per month) compared to ISIS 721744-CS5 study from Week 1 to Week 53

Switch patients only:

• The time-normalized number of Investigator-confirmed attack rate (per month) from Week 1 to Week 17

• The time-normalized number of Investigator-confirmed attack rate (per month) from Week 5 to Week 17

• Angioedema Quality of Life (AE-QoL) questionnaire total score at Week 17

• Treatment Satisfaction Questionnaire for Medication (TSQM-II) from Week 1 (Day1) to Week 17

• Injection site pain (ISP) assessment during Screening and Treatment Periods

• Treatment preference questionnaire at Week 17

Study description

Background summary

Hereditary angioedema is a rare genetic disorder that is characterized by disabling recurrent episodes of local skin swellings, painful abdominal attacks, and, occasionally, laryngeal attacks that can be life-threatening. The disorder is classified in 3 subtypes. Hereditary angioedema Type I (HAE-1) and Type II (HAE-2) are caused by an autosomal dominant mutation in the SERPING1 gene, resulting in either decreased levels of C1-INH (HAE-1) or loss-of-function of this protein (HAE-2). The third form of HAE is associated with normal levels and function of C1-INH (HAE-nC1-INH). This form is currently

categorized as 4 subtypes, with either specific genetic mutations in the Factor XII gene, the plasminogen gene, or the angiopoietin-1 gene, or due to an unknown cause. Extensive evidence from in vitro and in vivo studies supports the key role of bradykinin (BK) in HAE attacks, although the data linking HAE-nC1-INH with BK are less strong. Diagnosing HAE-nC1-INH can be challenging given the large heterogeneity of this patient population, the lack of diagnostic tests, and the fact that specific genetic mutations account only partially for the occurrence of this type of HAE. Recently, a threshold-stimulated kallikrein activity assay was shown to discriminate BK-mediated angioedema from histamine-mediated angioedema. This technique may, therefore, enhance the identification of HAE-nC1-INH patients that are likely to benefit from inhibition of the contact activation pathway.

This study involves the use of the investigational medicinal product known as ISIS 744721. When prekallikrein, a protein that is produced by the liver, is released into the blood stream, it can lead to HAE attacks. The study drug is designed to lower the amount of prekallikrein produced by the liver. The study is to assess if reducing the amount of prekallikrein can reduce HAE attacks.

Study objective

This study has been transitioned to CTIS with ID 2023-509201-77-00 check the CTIS register for the current data.

Primary Objective
To evaluate the safety of long-term dosing with donidalorsen in patients with HAE.

Secondary Objectives
To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the quality of life (QoL) of patients with HAE.

Exploratory Objectives
Further characterize the effects of donidalorsen on HAE attacks, additional Patient Reported Outcomes (PROs) and biomarkers.

Study design

This study is an Open-Label global study with donidalorsen conducted in multiple centers to evaluate the long-term safety and efficacy of donidalorsen in preventing angioedema attacks in patients with HAE-1 (Type I) and HAE-2 (Type II). There are 2 arms to this study; 1) patients who roll-over from another study of donidalorsen (OLE patients), and 2) patients who are not rolling over from another study of donidalorsen and were previously maintained on HAE prophylactic therapy (*Switch* patients) with lanadelumab, berotralstat

or C1-esterase inhibitor.
Following the Week 53 Treatment Period visit, patients will have the option of receiving donidalorsen in an Extended Treatment Period for up to an additional 104 weeks.

Intervention

OLE Patients:
Patients continue on their dosing schedule from ISIS 721744-CS5:
• Patients who received drug or placebo Q4W in ISIS 721744-CS5 will receive 80 mg of donidalorsen Q4W
• Patients who received drug or placebo Q8W in ISIS 721744-CS5 will receive 80 mg of donidalorsen Q8W unless they are not attack free for >= 8 weeks (Weeks 17-25 in ISIS 721744-CS5), in that case they will receive 80 mg of donidalorsen Q4W

Switch Patients:
All patients will receive 80 mg of donidalorsen Q4W.

Study burden and risks

Burden: during the study patients will be asked to come to the study center for 18 visits. Patients will be treated with donidalorsen every 4 or 8 weeks during the treatment period of about one year. Donidalorsen will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm.

The patient will be asked questions about their health and medications they are taking. A Quality of life questionnaire will be conducted. The HAE attack history of the patients will be recorded and their HAE attacks will be tracked daily by completing a questionnaire. Furthermore, patients need to inform their doctor of any adverse events they experienced. A physical examination and heart tracing (ECG) will be done and weight and vital signs will be measured. Also urine and blood tests will be done to see if patients are able to participate in the study and to check general health, pregnancy, pharmacodynamics, pharmocokinetics, inflammatory markers and antibodies in the body.

Risk: Possible side effects of the study drug and study procedures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Participants and, as applicable, legally authorized representatives (i.e., parent(s)/legal guardian), must provide written and signed informed consent form (ICF).
2. Participants must have access to, and the ability to use, >= 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a bradykinin receptor (BK) 2-receptor antagonist) to treat angioedema attacks

Open-Label Extension Participants ONLY:
3. Satisfactory completion of ISIS 721744-CS5 (randomized placebo-controlled index study) through Week 25 or participants who are allowed to exit ISIS 721744-CS5 study per protocol with an acceptable safety and tolerability profile

New (not previously on donidalorsen) Participants ONLY
4. Participants must be aged >= 12 years at the time of informed consent and, as applicable, assent
5. Participants must have a documented diagnosis of HAE-1/HAE-2
6. Participants must be on a stable dose (>= 12 weeks) of prophylaxis treatment with lanadelumab or berotralstat or C1-esterase inhibitor prior to the

Screening Period

Exclusion criteria

1. Have any new condition or worsening of an existing condition or change or anticipated change in medication

De-novo Participants:
2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III)
3. Anticipated change in the use of concurrent androgen or tranexamic acid prophylaxis used to prevent angioedema attacks
4. Any clinically-significant abnormalities in screening laboratory values
5. Malignancy within 5 years of Screening, except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma that has been successfully treated.
6. Hypersensitivity to the active substance (donidalorsen) or to any of the excipients
7. Treatment with another investigational drug (non-oligonucleotide) or biological agent within 1 month of Screening or 5 half-lives of investigational agent, whichever is longer
8. Recent history of, or current drug or alcohol abuse
9. Participated in a prior donidalorsen study
10. Exposure to any of the following medications:
Angiotensin-converting enzyme (ACE) inhibitors or any estrogen containing medications with systemic absorption
Oligonucleotides (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. This exclusion does not apply to vaccines

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-11-2022
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO Date:	20-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-02-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-11-2023
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	CTIS2023-509201-77-00
EudraCT	EUCTR2022-000757-93-NL
ClinicalTrials.gov	NCT05392114
CCMO	NL81330.000.22