A Randomized, Double Blind, Placebo Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second Generation Ligand Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

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The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE 1), HAE type 2 (HAE 2), or HAE with normal C1-inhibitor (C1-INH)....

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

Summary

ID

NL-OMON49723

Source
ToetsingOnline

Brief title
ISIS 721744-CS2

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: Hereditary Angioedema, ISIS 721744, Liver, Prekallikrein

Outcome measures

Primary outcome

The primary endpoint is the time-normalized number of HAE attacks (per month)

from Week 1 to Week 17.

Secondary outcome

Secondary endpoints include the following:

* The time-normalized number of HAE attacks (per month) from Week 5 to Week 17

* The time-normalized number of moderate or severe HAE attacks (per month) from

Week 5 to Week 17

* The number of patients with a clinical response (defined as a * 50%, * 70%,

or * 90% reduction from Baseline in HAE attack rate) by Week 17

* The number of HAE attacks requiring acute therapy from Week 5 to Week 17

* Cleaved high molecular weight kininogen (cHK) levels at Weeks 9 and 17

* PKK activity at Weeks 9 and 17

* Consumption of on-demand medication at Weeks 9 and 17

* Angioedema quality of life (AE-QoL) questionnaire score at Weeks 9 and 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 1 and 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) (Bissler et al. 1997).
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 (Maurer et al. 2018). 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 (Zuraw and Christiansen 2016). 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 (Lara*Marquez et al. 2018). 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

The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE 1), HAE type 2 (HAE 2), or HAE with normal C1-inhibitor (C1-INH).
The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE 1/HAE 2 or HAE with normal C1 INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.
The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide [ASO], including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on

relevant biomarkers and clinical outcomes, as appropriate.

Study design

This is a global, Phase 2a randomized, double-blind, placebo-controlled study designed to assess the clinical efficacy of ISIS 721744, a second-generation ligand-conjugated antisense inhibitor of prekallikrein, in patients with Hereditary Angioedema. The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE 1/HAE 2 in Part A or HAE nC1 INH in Part B). Part A is randomized, double blind, and placebo controlled; and Part B is open label. The study visit schedule and procedures are nearly identical in Part A and Part B.
In Part A, patients with HAE-1/HAE-2 will be randomized to subcutaneous (SC) injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.
The length of each patient*s participation in the study is approximately 8 months, which includes an up to 8-week Screening Period, a 12-week Treatment Period, and a 13-week Post Treatment Period. During Treatment Period patients will receive fixed SC doses of Study Drug (ISIS 721744 or Placebo) every 4 weeks.

This study includes an option for some study visits to occur at home with a home care nurse and may be considered for assessments and procedures at Weeks 3, 5, 9, 13, 17, 21, and 26 (at Screening and Week 1, patients must come to the study center for the assessments and procedures).

Eligible patients may elect to enroll in the open label extension (OLE) study (ISIS 721744-CS3).

Intervention

During the Treatment Period, study drug (ISIS 721744 or Placebo) will be administered as a single-SC injection every 4 weeks. For Part A, approximately 18 eligible patients (HAE 1 or HAE 2) will be randomized to SC injections of ISIS 721744 (80 mg/mL) or placebo in a 2:1 ratio. In Part B about 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 (80 mg/mL).

Study burden and risks

Burden: During the study patients will be asked to come to the study centre for 9 visit. Also, they will be contacted every week by phone by the study staff to

discuss their HAE attacks. Patients will be treated with ISIS 721744 or placebo every 4 weeks during the treatment period, meaning they will receive a subcutaneous injection in their abdomen, thigh or upper arm 4 times in total.
A demographic questionnaire, health and medication questionnaire and 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, height 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, post-menopausal status, pharmacodynamics, pharmocokinetics, inflammatory markers, antibodies and the activity of kallikrein protein and HAE related proteins in the body. If patients do not have HAE genetic diagnostic testing results prior to screening for participation in Part B, they will give a blood sample for genetic testing.
Patients will also be tested for HIV and hepatitis B and C.
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
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B);
- Participants must experience a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the investigator) during the screening period;
- Access to, and the ability to use, 1 or more acute medication(s) to treat angioedema attacks.

Exclusion criteria

- Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods.
- Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema.
- History of acquired coagulopathies or bleeding diathesis.
- Active infection with human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B.
- 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.
- Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening.
- Exposure to any of the following medications:
a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening.
b. Chronic prophylaxis with Lanadelumab within 10 weeks prior to Screening.
c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-06-2020
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	05-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-12-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-10-2020
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
EudraCT	EUCTR2019-001044-22-NL
CCMO	NL70862.000.19

Study results

Date completed:	29-01-2021
Results posted:	27-05-2022

First publication

15-02-2022