An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema

Published: 14-04-2020
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-517249-15-00 check the CTIS register for the current data. Primary Objective:To evaluate the safety of extended dosing, and alternative dosing and/or dose frequency with ISIS 721744 in patients...

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

Summary

ID

NL-OMON54255

Source
ToetsingOnline

Brief title
ISIS 721744-CS3

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

Primary Endpoint: Incidence and severity of treatment-emergent adverse events

(TEAE)

Secondary outcome

Secondary Endpoints:

- The time-normalized HAE attacks (monthly) by treatment

- Plasma PKK levels, plasma proenzyme activation and cHK levels

- Consumption of on-demand medications

- AE-QoL questionnaire score

Safety Endpoints:

- Laboratory tests

- Electrocardiograms (ECGs)

- Use of concomitant medications

- Vital signs

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

This study has been transitioned to CTIS with ID 2024-517249-15-00 check the CTIS register for the current data.

Primary Objective:
To evaluate the safety of extended dosing, and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE
Secondary Objective:
To evaluate the efficacy of extended dosing, and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE
Additional/Exploratory Objectives:
To evaluate the effects of ISIS 721744 on plasma prekallikrein (PKK) levels, plasma proenzyme activation and cleaved high molecular weight kininogen (cHK) levels.
To evaluate the effects of ISIS 721744 on the clinical and angioedema quality of life (AE-QoL) endpoints.
To evaluate PK exposure over time.

Sub-Study:
To evaluate the effect of chronic administration of ISIS 721744 on platelet

function.

Study design

Multi-center open-label extension study with ISIS 721744.
Dose Treatment Period 1 (Fixed Dosing Period): All patients will receive a subcutaneous (SC) injection of ISIS 721744 (80 mg) every 4 weeks for at least 12 weeks.
Dose Treatment Period 2 (Flexible Dosing Period): During the Treatment Period 2, if the patient is attack-free for >= 12 weeks after entering this OLE study, the Investigator can initiate a switch to 80 mg ISIS 721744 every 8 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks. For patients who are not attack free for >= 12 weeks the Investigator can initiate a switch to 100 mg ISIS 721744 every 4 weeks. The switch may begin at any Study Center visit starting at Week 17 . If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.
After completion of the 52-week Treatment Period, there is an option to participate in an Extended Treatment Period (up to an additional 156 weeks; Year 2, Year 3 and Year 4). There is a 12-week Follow-up Period after Year 1, Year 2, Year 3 or Year 4.
During the course of the study, the use of acute medication (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

Intervention

The total duration of the trial is 64 weeks with 52 weeks for the treatment phase and 12 weeks of follow-up. There is an option to participate in an Extended Treatment Period (up to an additional 156 weeks). The 12-week Follow-up Period will be conducted after the patient completes treatment

All patients will begin treatment with ISIS 721744 (80 mg) every 4 weeks for at least 12 weeks. Following completion of treatment period 1 and continuing through the extended treatment period, the patient and the Investigator (in consultation with the Sponsor Medical Monitor) can decide which option to choose:
Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks
Option 2: For patients who are attack free for >= 12 weeks, after entering this OLE study, the Investigator can initiate a switch to 80 mg every 8 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks.

Option 3: For patients who are not attack free for >= 12 weeks, after entering this OLE study, the Investigator can initiate a switch to 100 mg ISIS 721744 every 4 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.

Study burden and risks

Burden: During the study patients will be asked to come to the study centre for 16 visits. Patients will be treated with ISIS 721744 every 4 weeks for at least 12 weeks. ISIS 721744 will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm. At the end of this time, there are three treatment options:
Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks
Option 2: Switch to 80 mg every 8 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks.
Option 3: Switch to 100 mg ISIS 721744 every 4 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.

During the main study (year 1) and extension period (year 2, year 3 and year 4) there will be asked questions about your health and medications you 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

Public
Ionis Pharmaceuticals, Inc.

Gazelle Court 2855
Carlsbad CA 92010
US
Scientific

Ionis Pharmaceuticals, Inc.

Gazelle Court 2855
Carlsbad CA 92010
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Satisfactory completion of ISIS 721744-CS2 (index study) through Week 17 with an acceptable safety and tolerability profile, per Sponsor and Investigator judgement
3. Able and willing to participate in a 64-week study
4. Satisfy 1 of the following:
a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), 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 follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved), abstinent*, or, if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method from time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration
b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration
* Abstinence 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
5. Patients 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

Exclusion criteria

1. Have any new condition or worsening of an existing condition or change or anticipated change in medication or other reason, which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-11-2020
Enrollment:	7
Type:	Actual

Ethics review

Approved WMO

Date:	14-04-2020
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-06-2020
Application type:	First submission
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)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	28-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2024
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	CTIS2024-517249-15-00
EudraCT	EUCTR2020-000197-14-NL
CCMO	NL73400.000.20