An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II

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This study has been transitioned to CTIS with ID 2023-505904-41-00 check the CTIS register for the current data. Primary Objective: To assess the safety of long-term administration of KVD900 in adolescent and adult patients with HAE type I or II....

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON56365

Source
ToetsingOnline

Brief title
KONFIDENT-S

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Hereditary Angioedema; blood disease

Research involving

Human

Sponsors and support

Primary sponsor: KalVista Pharmaceuticals Ltd
Source(s) of monetary or material Support: KalVista Pharmaceuticals

Intervention

Keyword: Angioedema Attacks, Angioedema Type I or I, Hereditary, KVD900, Plasma Kallikrein Inhibitor

Outcome measures

Primary outcome

The proportion of patients with at least one AE in adolescent and adult

patients with HAE type I or II who have taken at least one dose of IMP.

Secondary outcome

PGI-C: Time to beginning of symptom relief defined as at least '' a little

better'' (2 time points in a row) within 12 hours of initial dose of IMP

administration.

PGI-S: Time to first incidence of 2 time points in a row decrease from baseline

within 12 hours of initial dose of IMP administration.

PGI-S: Time to HAE attack resolution, defined as ''none'' within 24 hours of

initial dose of IMP administration.

Study description

Background summary

Recurrent swelling in patients with HAE is predominantly a consequence of excessive generation of bradykinin due to dysregulated plasma kallikrein activity. Therefore, inhibition of plasma kallikrein activation has emerged as a target for the treatment of HAE. For example, treatment with ecallantide, a

specific inhibitor of plasma kallikrein given subcutaneously, led to significantly better treatment outcome scores compared with placebo. The oral small-molecule inhibitor of plasma kallikrein berotralstat and the plasma kallikrein monoclonal antibody lanadelumab have been shown to lower the rate of attacks in HAE patients compared with placebo, highlighting the role that plasma kallikrein plays in this disease. KVD900 has been shown in a range of nonclinical experiments to be a selective inhibitor of plasma kallikrein. This activity was confirmed in a completed trial (KVD900-101) of KVD900 in healthy volunteers at dose levels up to 600 mg. Within 1 hour of dosing mean protection of high molecular weight kininogen (HK) cleavage was >85%. Protection was maintained at >75% for 6 hours and >45% for 10 hours at a dose of 600 mg. Forty percent (40%) HK protection is achieved by C1-INH levels typically present in control plasma samples. It is therefore a plausible hypothesis that treatment with a single dose of KVD900 600 mg may halt the progression of HAE attacks. This hypothesis was tested in a Phase 2 trial (KVD900-201) for the on-demand treatment of HAE attacks. The trial was a cross-over in which 53 patients with either type I or II HAE completed. Results showed a significant difference between 600 mg KVD900 and placebo for the primary endpoint of time to conventional treatment use and secondary endpoints of attack improvement using Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S), and a composite visual analogue scale (VAS) measuring symptoms of the attack. The clinical efficacy of 2 dose levels of KVD900 will be investigated in a Phase 3 trial, KVD900-301, a double-blind, randomized, placebo-controlled, multicenter, clinical trial in patients 12 years of age or older with HAE type I or II. Patients will be randomized to 6 treatment sequences in a 3-way crossover design. Eligible attacks will be treated with placebo, 300 mg, or 600 mg KVD900 per attack (with the option for patients to take a second dose of IMP to treat each attack) with a minimum 48-hour washout period between attacks. The current trial, KONFIDENT-S, is an open-label, multicenter extension trial to evaluate the long-term safety of a single dose of 600 mg KVD900 (with the option for patients to take a second dose of IMP to treat each attack) in patients who are 12 years of age or older with HAE type I or II. Long-term efficacy is also being evaluated as a secondary objective. The trial will be conducted in parallel with KVD900-301.

Study objective

This study has been transitioned to CTIS with ID 2023-505904-41-00 check the CTIS register for the current data.

Primary Objective: To assess the safety of long-term administration of KVD900 in adolescent and adult patients with HAE type I or II.
Secondary Objectives:
• To assess the long-term efficacy of KVD900 in the treatment of attacks in adolescent and adult patients with HAE type I or II.
• To assess the safety and efficacy of KVD900 when used as short-term

prophylaxis in adolescent and adult patients with HAE types I or II.

Study design

KONFIDENT-S is an open-label, multicenter extension trial to evaluate the long-term safety of KVD900 in patients who are 12 years of age or older with HAE type I or II.
This trial will be conducted on an outpatient basis and includes in-clinic or home health visits and televisits. A televisit can be conducted via a telephone call or via an interactive audio/video system. The maximum duration of this trial for individual patients will be 2 years.

Intervention

• KVD900 300 mg Film-Coated Tablet.
• IMP will be packaged in a carton containing 4 drawers with 6 tablets (300 mg each) in each drawer. Resupply will occur on an as-needed basis.
• For the on-demand treatment of HAE attacks, patients will treat each attack with a single dose of 2 x 300 mg (600 mg total) KVD900. A second dose is allowed if separated by at least 3 hours following the first dose in cases where symptoms persist without improvement.
• For short-term prophylaxis prior to undergoing surgical, dental, or medical procedures, patients will be permitted to take up to 3 doses of KVD900 in a 24-hour period,
• No IMP dose modifications are allowed in this trial except for the protocol-allowed dosing for short-term prophylaxis.

Study burden and risks

Study subjects are expected to undergo the assessments and tests as described in the table 1 of the study protocol. These procedures include physical exam, vital signs, demographic and medical history, ECG, questionnaire, blood and urine tests, pregnancy tests in women of childbearing potential, and completion of eDiary. The study medication is a non-registered medication. Possible known side effects are described in the Investigators Brochure and patient information and can also occur during this study. There is also a risk that unknown side effects occur and there is a chance that the treatment will not be efficacious for the patient.
The KONFIDENT-S trial is considered to have a positive benefit-risk balance.

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)
Elderly (65 years and older)

Inclusion criteria

Patients may roll over from KVD900-301.
1) Confirmed diagnosis of HAE type I or II at any time in the medical history
2) Patient has had at least 2 documented HAE attacks within 3 months prior to the Enrollment Visit.
3) If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Enrollment Visit.
4) Male or female patients 12 years of age and older.
5) Patients must meet the contraception requirements.
6) Patients must be able to swallow trial tablets whole.
7) Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary.
8) Investigator believes that the patient is willing and able to adhere to all protocol requirements.
9) Patient provides signed informed consent or assent (when applicable). A

parent or LAR must also provide signed informed consent when required.

Exclusion criteria

1) Discontinued from the KVD900-301 trial for reasons of noncompliance, withdrawal of consent, or safety. 2) Presence of any safety concerns that would preclude participation in the open-label trial as determined by the investigator. 3) Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria. 4) A clinically significant history of poor response to bradykinin receptor-2 (BR2) blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. 5) Use of attenuated androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone), or anti-fibrinolytics (e.g., tranexamic acid) within 28 days prior to the Enrollment Visit. 6) Use of ACE inhibitors within 7 days prior to the Enrollment Visit. 7) Any estrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Enrollment Visit. 8) Inadequate organ function, including but not limited to: a) Alanine aminotransferase (ALT) >2x ULN b) Aspartate aminotransferase (AST) >2x ULN c) Bilirubin direct >1.25x ULN d) INR >1.2 e) Clinically significant hepatic impairment defined as a Child-Pugh B or C 9) Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial. 10) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. 11) Known hypersensitivity to KVD900 or to any of the excipients. 12) Participation in any gene therapy treatment or trial for HAE. 13) Participation in any interventional investigational clinical trial, including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to the Enrollment Visit. 14) Any pregnant or breastfeeding patient.

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):	26-07-2023
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Sebetralstat
Generic name:	KVD900

Ethics review

Approved WMO Date:	22-08-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam

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Approved WMO
Date: 12-06-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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Approved WMO
Date: 19-07-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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Approved WMO
Date: 04-08-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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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
EU-CTR	CTIS2023-505904-41-00
EudraCT	EUCTR2021-001176-42-NL
CCMO	NL80192.018.22