A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels 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 I

Published: 28-03-2022
Last updated: 17-01-2025

Primary Objective: To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.Secondary Objective: To investigate the safety and tolerability of KVD900.

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

Summary

ID

NL-OMON51849

Source
ToetsingOnline

Brief title
KONFIDENT (KalVista KVD900-301) Study

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

• 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 the first IMP

administration.

Secondary outcome

Key Secondary Endpoints

• PGI-S: Time to first incidence of decrease from baseline within 12 hours of

the first IMP administration.

• PGI-S: Time to HAE attack resolution defined as *none* within 24 hours of the

first IMP administration.

Secondary Endpoints

• PGI-C: Proportion of attacks with beginning of symptom relief defined as at

least *a little better* (2 time points in a row) within 4 hours and within 12

hours of the first IMP administration.

• PGI-C: Time to at least *better* within 12 hours of the first IMP

administration.

• PGI-S: Time to first incidence of decrease from baseline within 24 hours of

the first IMP administration.

• Composite VAS: Time to at least a 50% decrease from baseline (3 time points

in a row) within 12 hours and within 24 hours of the first 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 current trial (KVD900-301) will evaluate two dose levels of KVD900 (with the option for patients to take a second dose of IMP to treat each attack) for the on-demand treatment of HAE attacks under randomized, double-blind, placebo-controlled conditions. Ex vivo testing suggests that a dose of 300 mg may also bring relief to an attack of HAE. The randomized, double-blind, placebo-controlled, three-way crossover design of this trial has been chosen as an appropriate test of that hypothesis.
Adolescents (12 to 17 years old) will be included in this trial. A population PK model has been built which predicted KVD900 exposure in a simulation population containing 600 subjects (400 females and 200 males) 12 to 17.9 years of age with body weight ranging from 31.0 to 93.3 kg. The population PK model predicted overall KVD900 exposure in an adolescent population (12 to 17 years old) to be similar to that in healthy adults for a single 600 mg dose of KVD900 under fasted conditions.

Study objective

Primary Objective: To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.
Secondary Objective: To investigate the safety and tolerability of KVD900.

Study design

This is a double-blind, randomized, placebo-controlled, multicenter clinical trial in patients 12 years 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 initially be treated with a single dose of placebo, 300 mg, or 600 mg KVD900 per attack. If needed (as determined by the patient), an additional dose of IMP may be administered for each attack.
The trial duration from screening through to the final visit, including the treatment of 3 eligible attacks during the treatment period, is approximately 25 weeks for each randomized participant.

Intervention

Each participant will receive the following treatments with the option for participant to take a second dose of IMP to treat each attack:
• 300 mg KVD900 (1 x 300 mg tablet plus 1 matching placebo tablet)
• 600 mg KVD900 (2 x 300 mg tablets)
• 2 matching placebo tablets.

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.
KVD900-301 study is considered to have a positive benefit-risk balance.

Contacts

Public
KalVista Pharmaceuticals Ltd

Porton Science Park, Bybrook Road, Porton Down -
Salisbury SP4 0BF
GB
Scientific
KalVista Pharmaceuticals Ltd

Porton Science Park, Bybrook Road, Porton Down -
Salisbury SP4 0BF
GB

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

1) Male or female patients 12 years of age and older.

2) Confirmed diagnosis of HAE type I or II at any time in the medical history.
3) Patient has access to and ability to use conventional on-demand treatment for HAE attacks.
4) If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies. They must be on a stable dose and regimen for at least 3 months prior to the Screening Visit and be willing to remain on a stable dose and regimen for the duration of the trial.
5) Patient's last dose of attenuated androgens was at least 28 days prior to randomization.
6) Patient:
a) has had at least 2 documented HAE attacks within 3 months prior to randomization; or
b) is a completer of the KVD824-201 trial within 3 months prior to randomization and meets all
other entry criteria to enroll in KVD900-301.
7) Patients must meet the contraception requirements.
8) Patients must be able to swallow trial tablets whole.
9) Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the electronic diary (eDiary).
10) Investigator believes that the patient is willing and able to adhere to all protocol requirements.
11) Patient provides signed informed consent or assent (when applicable). A parent or legally authorized representative (LAR) must also provide signed informed consent when required.

Exclusion criteria

1) 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.
2) 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.
3) Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization.
4) Any estrogen containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit.
5) Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers.
6) Inadequate organ function, including but not limited to:
a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
b) Aspartate aminotransferase (AST) >2x ULN

c) Bilirubin direct >1.25x ULN
d) International normalized ratio (INR) >1.2
e) Clinically significant hepatic impairment defined as a Child-Pugh B or C
7) 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.
8) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator.
9) Known hypersensitivity to KVD900 or placebo or to any of the excipients.
10) Prior participation in trial KVD900-201.
11) Participation in any gene therapy treatment or trial for HAE.
12) Participation in any interventional investigational clinical trial (with the exception of KVD824-201), including an investigational COVID 19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to screening.
13) Any pregnant or breastfeeding patient.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-09-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	KVD900
Generic name:	KVD900

Ethics review

Approved WMO Date:	28-03-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

	1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2021-001226-21-NL
ClinicalTrials.gov	NCT05259917
CCMO	NL80191.018.22

Study results

Results posted: 20-06-2024

First publication
31-05-2024