ISRCTN14762022 https://doi.org/10.1186/ISRCTN14762022

A study to evaluate if different doses of KVD900 are safe and effective in treating attacks in patients with hereditary angioedema

Submission date
22/03/2022

Recruitment status
No longer recruiting

Registration date
16/09/2022

Overall study status
Completed

Last Edited
10/06/2024

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Hereditary angioedema is a disorder characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body to develop swelling are the limbs, face, intestinal tract, and airway.
This study is being done to understand how well KVD900 300 mg or KVD900 600 mg works against placebo to bring relief from an attack of hereditary angioedema (HAE).

Who can participate?
Approximately 114 patients with HAE Type I or II will be enrolled into the trial. Patients will be enrolled from several different countries.

What does the study involve?
In this study every patient will treat one attack with 300 mg KVD900, one attack with 600 mg of KVD900 and one attack with placebo. The order the patients use the treatments will be assigned by chance. During each treated attack the patients will answer several questions regarding their symptoms during the course of the treatment.
Participants will be asked to attend the site approximately for 2 visits and have 4 tele visits. It is anticipated that it will take approximately 25 weeks for each patient to complete the screening assessments and treat 3 eligible attacks. In addition to the questions regarding the HAE attack symptoms and effectiveness of the treatments, patients will undergo routine safety assessments, such as laboratory assessments and physicals.

What are the possible benefits and risks of participating?
Benefits:
Taking part in this study may or may not help to treat HAE. Participants' health could improve, stay the same, or get worse. However, the data we get during this study may help doctors learn more about the study drug and the disease and this may help future patients with HAE.
Risks:
KalVista is still building its knowledge about the safety of KVD900. The study drug has so far only been used in small groups of healthy people and patients with HAE, therefore some side

effects are not yet known. The most common side effect experienced to date has been a headache.

Where is the study run from?
Barts Health NHS Trust
Leeds Teaching Hospitals NHS Trust
Frimley Health NHS Trust
University Hospitals Birmingham NHS Foundation Trust
Cardiff and Vale University Health Board

When is the study starting and how long is it expected to run for?
January 2022 to December 2023

Who is funding the study?
KalVista Pharmaceuticals Ltd (UK)

Who is the main contact?
Dr Sorena Kiani-Alikhan, skiani@nhs.net

Contact information

Type(s)
Scientific

Contact name
Mr Michael Smith

Contact details
KalVista Pharmaceuticals Ltd
Porton Science Park
Bybrook Road
Porton Down
Salisbury
United Kingdom
SP4 0BF
+18018597818
mds@kalvista.com

Type(s)
Principal investigator

Contact name
Dr Sorena Kiani-Alikhan

Contact details
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

+44 20 7794 0500 Ext: 34906
skiani@nhs.net

Additional identifiers

Clinical Trials Information System (CTIS)
2021-001226-21

Integrated Research Application System (IRAS)
1004998

ClinicalTrials.gov (NCT)
NCT05259917

Protocol serial number
KVD900-301, IRAS 1004998, CPMS 51516

Study information

Scientific Title
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 II

Acronym
KONFIDENT

Study objectives
To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.
To investigate the safety and tolerability of KVD900.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/05/2022, West of Scotland REC1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 3140213; WoSREC1@ggc.scot.nhs.uk),), ref: 22/WS/0042

Study design
Interventional double-blind randomized cross-over placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hereditary angioedema (HAE) type I or type II.

Interventions
Patients will be assigned to receive 3 treatments in randomized, double-dummy blinded, crossover fashion based on their assignment to 1 of 6 treatment sequences. Randomization will occur in a 1:1:1:1:1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment sequence. Each patient will receive the following treatments:

• 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

Patients will treat each eligible attack with up to 2 doses of IMP, administered at least 3 hours apart. The second dose, if taken, will be the same assigned treatment as the first dose.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
KVD900, sebetralstat

Primary outcome(s)
PGI C: Time to beginning of symptom relief defined as at least “a little better” (2 timepoints in a row) within 12 hours of the first IMP administration.

Key secondary outcome(s))
Current secondary outcome measures as of 26/10/2023:

1. PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.
2. PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration
3. 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
4. PGI:C Time to at least "better" (2 time points in a row) within 12 hours of the first IMP administration.
5. PGI:S: Time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration.
6. 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

———

Previous secondary outcome measures:

1. PGI-S: Time to first incidence of decrease from baseline within 12 hours of the first IMP administration

2. PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration
3. 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
4. PGI-C: Time to at least "better" within 12 hours of the first IMP administration
5. PGI-S: Time to first incidence of decrease from baseline within 24 hours of the first IMP administration
6. 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

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 26/10/2023:

1. Male or female patients 12 years of age and older with a weight of >30 kg
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:
6.1. Has had a least two documented HAE attacks within 3 months prior to screening or randomisation; or
6.2. 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.

———

Previous inclusion criteria as of 04/11/2022:

1. Male or female patients 12 years of age and older with a weight of >30kg
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:
6.1. Has had at least two documented HAE attacks within 3 months prior to randomization; or
6.2. 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.

———

Previous inclusion criteria:

1. Male or female patients 12 years of age and older with a weight of >30kg
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 these medicines indicated for HAE: intravenous (iv) or sc plasma-derived C1-INH, and/or lanadelumab, 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 has had at least 2 documented HAE attacks within 3 months prior to randomization.
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.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 years

Sex
All

Total final enrolment

Key exclusion criteria

Current exclusion criteria as of 04/11/2022:

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:
6.1. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
6.2. Aspartate aminotransferase (AST) >2x ULN
6.3. Bilirubin direct >1.25x ULN
6.4. International normalized ratio (INR) >1.2
6.5. 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 the investigational drug prior to screening.
13. Any pregnant or breastfeeding patient.

———

Previous 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. Use of strong cytochrome P450 3A4 (CYP3A4) inhibitors and inducers during participation in

the trial, starting within 5 half-lives of the Screening Visit.
6. Inadequate organ function, including but not limited to:
6.1. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
6.2. Aspartate aminotransferase (AST) >2x ULN
6.3. Bilirubin direct >1.25x ULN
6.4. International normalized ratio (INR) >1.2
6.5. 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, including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of the investigational drug prior to screening.
13. Any pregnant or breastfeeding patient.

Date of first enrolment
23/02/2022

Date of final enrolment
11/08/2023

Locations

Countries of recruitment
United Kingdom

Australia

Bulgaria

Canada

France

Germany

Greece

Hungary

Israel

Italy

Japan

Netherlands

New Zealand

North Macedonia

Poland

Portugal

Romania

Slovakia

Spain

United States of America

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1FR

Study participating centre
Frimley Health NHS Trust
Frimley Park Hospital
Portsmouth Road
Camberley
United Kingdom
GU16 7UJ

Study participating centre
Leeds Teaching Hospital NHS Trust
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS7 9AP

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Birmingham Heartlands Hospital

Bordesley Green East
Birmingham
United Kingdom
B15 2GW

Study participating centre
Cardiff and Vale University Health Board
Cardiff and Vale UHB Headquarters
University Hospital of Wales (UHW)
Heath Park
Cardiff
Cardiff
United Kingdom
CF14 4XW

Sponsor information

Organisation
KalVista Pharmaceuticals Ltd

Funder(s)

Funder type
Industry

Funder Name
KalVista Pharmaceuticals Ltd

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 03/03/2023:
The datasets generated during the KVD900 (sebetralstat) trials are not expected to be made available due to the stage of development (i.e., pre-marketing authorization) and to ensure the protection of individual patient data. Due to the rarity of the disease, it may be possible to link anonymized patient data back to individual patients. Therefore, only aggregate data will be shared through regular publicly available methods (e.g., ClinicalTrials.gov, euclinicaltrials.eu, scientific publications).

Previous IPD sharing statement:
Independent researchers will be permitted to use anonymised data collected from participants during this study to conduct additional scientific research, which may be unrelated to the study medication. The data provided to external researchers will not include identifiable information. All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		31/05/2024	10/06/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes