A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II

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Primary Objective:• To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of hereditary angioedema (HAE).Secondary Objectives:• To investigate the safety and tolerability of KVD900…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON48423

Source
ToetsingOnline

Brief title
KVD900-201

Condition

- Autoimmune disorders

Synonym
Hereditary Angioedema Type I or II, swelling of tissues

Research involving
Human

Sponsors and support

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

Intervention

Keyword: angioedema attacks, hereditary angioedema, KVD900

Outcome measures

Primary outcome

Primary Efficacy Endpoints:

• Time to use of conventional attack treatment.

Secondary outcome

Secondary Efficacy Endpoints:

• Proportion of HAE attacks that progress by one level or more on the 5LS or

that require conventional attack treatment within 12h of study drug.

• Time between treatment and (1) progression of global attack severity on the

5LS by one level or more, or (2) use of conventional attack treatment,

whichever comes first within 12h.

Exploratory Endpoints:

• Cumulative global attack severity on the 5LS following study drug expressed

as area under the curve (AUC) for KVD900 600 mg vs. placebo.

• Proportion of HAE attacks that require conventional attack treatment.

• Proportion of HAE attacks that are rated *worse* or *much worse* on the TQ.

Proportion of HAE attacks that are rated *better* or *much better* on the TQ.

• Time from study drug administration to complete HAE attack resolution (rating

of none) on global attack severity scale (5LS).

• Time to HAE attack being rated worse or much worse on the TQ.

• Time to HAE attack being rated better or much better on the TQ.

Study description

Background summary

Bradykinin is formed by the action of a protease enzyme, plasma kallikrein (PKa), on a precursor molecule, kininogen, leading to the release of active bradykinin into the circulation. In the absence of the natural inhibitor of PKa, C1 inhibitor (as is the case in HAE), excessive bradykinin activity triggers the HAE attacks. It is therefore logical to target inhibition of PKa as a treatment strategy in HAE.
In study KVD900-101, the pharmacodynamic profile of KVD900 tablets resulted in 95% inhibition of plasma kallikrein within 30 minutes, a timeframe that potentially compares favorably to approved injected therapies. KVD900 displays a profile well-suited for use as an on-demand therapy for HAE attacks, with a combination of rapid and high uptake into the plasma resulting in fast and strong inhibition of plasma kallikrein.
It is therefore a plausible hypothesis that treatment with a single dose of KVD900 600 mg may halt the progression of HAE attacks.

Study objective

Primary Objective:
• To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of hereditary angioedema (HAE).
Secondary Objectives:
• To investigate the safety and tolerability of KVD900.
• To investigate the pharmacokinetic (PK) profile of KVD900 when taken during the intercritical period between HAE attacks.
• To investigate the pharmacodynamic (PD) profile of KVD900 in reducing the concentration of residual cleaved high molecular weight kininogen (HK) during the intercritical period between HAE attacks.
• To investigate the PD profile of KVD900 in reducing activated plasma enzyme activity during the intercritical period between HAE attacks.

Study design

This is a phase 2, two-part, two-sequence, two-period (2x2) cross-over clinical trial: Subjects with HAE type I or II will be recruited through HAE treatment centres in Europe.
In Part 1, subjects will receive a single oral dose of 600 mg KVD900 to investigate the safety, PK and PD of KVD900 during the intercritical period between HAE attacks.
Eligible adult subjects >=18 years old will undergo a screening assessment for study inclusion, receive study drug, followed by a 4h, in-clinic, safety and PK / PD assessment.
In Part 2, the subjects will be randomized 1:1 to 2 treatment sequences. This part of the study will be conducted away from the clinic or hospital.
In Sequence 1 (study arm 1) subjects will receive a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a second single dose of placebo to treat the second eligible HAE attack.
In Sequence 2 (study arm 2) subjects will receive a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack,subjects will receive a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.
A minimum of 48-hour washout period required between each dose of study drug.
Laryngeal or facial attacks are not eligible for treatment. HAE attacks must be treated within the first hour of onset and before reaching severe on the global attack severity scale. Subjects must also be able to identify the start of a HAE attack. Upon onset of the eligible HAE attack, subjects will notify the dedicated study physician or qualified designee with a description of the HAE attack. The dedicated study physician or qualified designee will confirm eligibility of the HAE attack and agree to study drug being administered. HAE attacks require documentation, on the Subject Diary, of attack location, attack symptoms, time of onset, attack severity, and time of last substantial meal prior to dosing. Subjects will take study drug, as instructed, and will complete timed assessments of their HAE attack symptoms for a 48h period as documented below in Table 1 (S) from the protocol. The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject*s safety and wellbeing. Subjects will be instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are to contact the dedicated study physician or qualified designee or contact the nearest emergency service. The dedicated study physician or qualified designee will be available 24h/day and 7 days/week to receive subject calls.
Subjects will return to the clinic following the first HAE attack, prior to the second HAE attack, to undergo safety checks including adverse event (AE) reporting, vital sign recording, and Subject Diary review.
Once two HAE attacks have been treated in Part 2, the subject will return to

the clinic to undergo final safety checks including AE reporting, vital sign recording and blood sampling for laboratory safety measurements.
Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject*s usual treatment regimen, or are deemed ineligible for study drug treatment, or are associated with laryngeal or facial symptoms. Prior to use of conventional attack treatment, subjects will notify the dedicated study physician or qualified designee who will confirm conventional treatment is appropriate per protocol and subject report of symptom severity. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH intravenous [iv] or icatibant).

Intervention

Non clinical interventions/procedures:
Study Informed Consent,
Review of Inclusion/Exclusion Criteria,
Demographic data and medical history,
Concomitant medications

Clinical interventions/procedures:
Height, Weight and Physical
Vital Signs
ECG
Pregnancy test
Blood sampling (various including PK)

Study burden and risks

In contrast to other available on-demand treatments for HAE attacks, KVD900 is orally-administered, is rapidly absorbed from the tablet formulation and has been shown in healthy volunteers to have a time profile for kallikrein inhibition (30 min to 10h post-dose) which is appropriate for the treatment of this condition. A single dose of 600 mg may be reasonably expected to bring relief to or halt the progression of an attack of HAE. The double-blind, placebo-controlled crossover design of Part 2 of the study has been chosen as an appropriate initial test of that hypothesis.
Good Laboratory Practice (GLP) repeat dose toxicology studies in the rat (28 day) and monkey (35 day) were conducted to support the clinical development of KVD900. The No-observed Adverse Effect Levels (NOAELs) were 300 mg / kg / day in the rat and 50 mg / kg / day in the monkey.
In the completed healthy volunteer study, single doses of 600 mg were well tolerated with no serious adverse events (SAEs) or deaths. There were 26 adverse events (AEs) shared by 19 of 84 subjects in all parts of the study.
All AEs were mild, except for one AE (headache) in the 10 mg cohort of Part A,

which was considered moderate. A total of 9 events were considered by the Investigator to be possibly or probably related to KVD900 treatment: dizziness (x1) in the 5 mg cohort of Part A, and headache (x4), fatigue (x2), and lethargy (x2) with 600 mg in subjects of Part C. All AEs had resolved by the end of the study.
The two-part design of the current study has been chosen in order to confirm under open-label, clinic-supervised conditions (Part 1) that administration of a single 600 mg dose of KVD900 is tolerated by individual subjects before that dose is administered away from the clinic or hospital in Part 2 of the study. Further safety features of Part 2 include the exclusion of laryngeal or facial attacks and the availability of conventional attack treatment from 4h after study treatment, or earlier, as warranted.
Overall, study KVD900-201 is considered to have a positive benefit-risk balance
Electrocardiogram (ECG)
This test is also non-invasive and not painful. The electrocardiogram (ECG) is a tracing of patients heart beating, made by recording tiny changes of electricity produced by their heart at the surface of the skin. To record these changes electrode stickers will be put on patients chest with wires attached to them. It will take about 5-10 minutes
Blood sample analysis
Blood samples will be collected for examination at each visit. Collecting the blood samples might cause discomfort during the study. An anaesthetic cream can be apply to make the area numb and reduce the discomfort.

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

1. Male or female adult subjects 18 years of age and older.
2. Confirmed diagnosis of HAE type I or II at anytime in the medical history:
3. At least 3 documented HAE attacks in the past 93 days, as supported by medical history.
4. Access to and ability to use conventional attack treatment for attacks of HAE.
5. Adequate organ functions as defined below:
a. Hemoglobin within normal range;
b. International normalized ratio (INR)< 1.2;
c. Activated partial thromboplastin time (aPTT) <= upper limit of normal (ULN);
d. Creatinine < 1x ULN;
e. Creatinine clearance (CrCl) >= 60 mL/min;
f. Alanine aminotransferase (ALT) <= 2x ULN;
g. Aspartate aminotransferase (AST) <= 2x ULN;
h. Total bilirubin <= 1.5x ULN;
i. Leucocytes <= 1.5x ULN;
j. Thrombocytes <= 1.5x ULN.
6. Female of childbearing potential must agree to use highly effective birth control from the Screening visit until the end of the trial follow-up procedures.
7. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study.
8. Males with female partners of childbearing potential must agree to be abstinent or else use a highly effective method of birth control as defined in inclusion criterion 6 from the Screening visit until the end of the trial follow-up procedures.
9. Provide signed informed consent and are willing and capable of complying with study requirements and procedures.

Exclusion criteria

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE type III), idiopathic angioedema, or
angioedema associated with urticaria.
2. Current use of C1INH, androgens, lanadelumab or tranexamic acid for HAE prophylaxis.
3. Use of angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within
93 days prior to initial study treatment.
4. Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterones, testosterone) or antifibrinolytics within 30 days prior to initial study treatment.
5. Use of lanadelumab within 10 weeks prior to initial study treatment
6. Use of strong CYP3A4/CYP2C9 inhibitors and inducers during participation in the trial.
Note: These medications include but are not limited to the following: cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, boceprevir, telaprevir, troleandomycin, clarithromycin, carbamazepine, enzalutamide, mitotane, phenytoin,
phenobarbital, fluconazole, isoniazid, metronidazole, paroxetine, sulfamethoxazole, rifampicin, St. John*s Wort, diltiazem, idelalisib, nefazodone and nelfinavir.
7. Clinically significant abnormal electrocardiogram (ECG) at Visit 1 and pre-dose at Visit 2. This includes, but is not limited to, a QTcF > 470 msec (for women) or > 450 msec (for men), a
PR > 220 msec or ventricular and/or atrial premature contractions that are more frequent than occasional and/or occur as couplets or higher in grouping.
8. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular abnormality.
9. Any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory, cardiovascular) or significant disease or disorder which, in the opinion of the Investigator, would jeopardize the
safety of the subject by taking part in the trial.
10. History of substance abuse or dependence that would interfere with the completion of the study, as determined by the Investigator.
11. Known lactose allergy or intolerance.
12. Known hypersensitivity to KVD900 or placebo or to any of the excipients.
13. Participation in an interventional investigational clinical study within 93 days or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to initial study treatment.

14. Any pregnant or breast-feeding subject.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-07-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KVD900
Generic name:	KVD900

Ethics review

Approved WMO Date:	25-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2019

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2019
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	EUCTR2018-004489-32-NL
CCMO	NL69091.018.19