



Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Ekterly 300 mg film-coated tablets

sebetralstat

PL 46326/0001

KalVista Pharmaceuticals Ltd

LAY SUMMARY

Ekterly 300 mg film-coated tablets. sebetralstat

This is a summary of the Public Assessment Report (PAR) for Ekterly 300 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Ekterly in this lay summary for ease of reading.

For practical information about using Ekterly, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Ekterly and what is it used for?

This application is full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Ekterly is a medicine that contains the active substance sebetralstat. Ekterly is used to treat attacks of hereditary angioedema in adults and adolescents aged from 12 years.

What Hereditary Angioedema is

Hereditary angioedema is a condition that often runs in families. In hereditary angioedema the blood does not have enough of a protein called C1 inhibitor, or the protein does not work properly. This leads to too much of the enzyme 'plasma kallikrein', which in turn increases the levels of 'bradykinin' in the bloodstream. Too much bradykinin leads to attacks of swelling and pain in different parts of the body.

How does Ekterly work?

Ekterly works by blocking the activity of plasma kallikrein and helps reduce the levels of bradykinin. When taken at the start, or during an attack, this will stop further progression of the attack and the symptoms of swelling and pain.

How is Ekterly used?

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is taken by mouth (for oral use).

Adults and adolescents aged 12 years and over:

The recommended dose is ONE tablet to be taken at the earliest sign that a patient is having an attack. The tablet should be swallowed whole with some water, if required. The tablet can be taken with or without food. An additional dose of ONE tablet may be taken if symptoms persist.

If the patient is taking strong CYP3A4 inhibitors such as itraconazole the patient's doctor will prescribe taking a single tablet when treating an attack. If the patient is taking strong or moderate CYP3A4 inducers such as phenytoin or efavirenz the doctor will prescribe taking three tablets

together when treating an attack. No more than three tablets should be taken in 24 hours (i.e. patients taking strong or moderate CYP3A4 inducers).

Use in children

Ekterly is not recommended for use in children under 12 years of age because it has not been studied in these patients.

For further information on how Ekterly is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Ekterly have been shown in studies?

The pivotal KONFIDENT trial showed efficacy in favour of sebetralstat over placebo (dummy treatment) in both main and secondary measures of effectiveness. The main measure of effectiveness was time to beginning of symptom relief following an attack of hereditary angioedema (HAE), the secondary measures were on the time to reduction in severity and time to complete attack resolution.

Key results main measure of effectiveness

Time to symptom relief favoured sebetralstat, with a median time of 1.61 hours for the 300 mg dose, compared with 6.72 hours for placebo.

Key results secondary measures of effectiveness

Time to reduction in severity was also shorter for attacks treated with sebetralstat, with a median time of 9.27 hours for the 300 mg dose and greater than 12 hours (not evaluable) for placebo.

More attacks reached complete HAE attack resolution within 24 hours of the first Ekterly administration in the 300 mg dose group (37 [42.5%] attacks) than in the placebo group (23 [27.4%] attacks).

What are the possible side effects of Ekterly?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Ekterly approved?

It was concluded that Ekterly has been shown to be effective when used to treat attacks of hereditary angioedema in adults and adolescents aged from 12 years. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Ekterly has been authorised as a UK Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Ekterly?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Ekterly. The RMP details the important risks of Ekterly, how these risks can be minimised, any uncertainties about Ekterly (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Ekterly:

Table SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Drug-drug interaction (sebetralstat as an object) with CYP3A4 inducers Lactic acidosis secondary to transporter-mediated interactions (sebetralstat as a precipitant)
Missing information	Use in patients with severe hepatic impairment Use in pregnancy and lactation Use in paediatric patients <12 years of age

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Ekterly are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Ekterly

A marketing authorisation application for Ekterly was received 23 September 2024, and a marketing authorisation was granted in the United Kingdom (UK) on 15 July 2025.

The full PAR for Ekterly follows this summary.
This summary was last updated in November 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Ekterly 300 mg film-coated tablets (PL 46326/0001) could be approved.

The product is approved for the following indication:

For the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.

Mechanism of action

Sebetralstat is a competitive, reversible inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high molecular weight kininogen (HK) releasing bradykinin (BK) which increases vascular permeability through activation of BK receptors causing oedema. Sebetralstat inhibits the cleavage of HK to BK, preventing activation of the BK receptors and halting the progression of HAE attacks. Sebetralstat also inhibits the positive feedback mechanism of the kallikrein kinin system by plasma kallikrein, thereby reducing factor XIIa and additional plasma kallikrein generation.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of the Access Consortium, which consists of the regulatory authorities of Australia (TGA) Canada (Health Canada), Singapore (HSA), Switzerland (Swissmedic) and the MHRA (UK). Work-sharing for this application was conducted between Australia (TGA), Singapore (HSA), Switzerland (Swissmedic) and UK (MHRA). Each regulator made independent decisions regarding approval of the application.

This application was evaluated for fulfilment of orphan designation criteria. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

On 10 June 2024, the MHRA issued a positive opinion following assessment of MHRA-100544-PIP01-22-M02-C1. No PIP studies were due to be initiated or completed between compliance verification and submission of the marketing authorisation application.

The PIP application included a licensing authority decision on the agreement of a waiver in

The paediatric subset(s):	The paediatric population from birth to less than 2 years of age
Pharmaceutical form(s):	Age appropriate oral solid dosage form. film-coated tablet
Route(s) of administration:	Oral use

Reason for granting waiver: on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation application for Ekterly was received on 23 September 2024, and marketing authorisation was granted in the United Kingdom (UK) on 15 July 2025.

II QUALITY ASPECTS

II.1 Introduction

What Ekterly contains

The active substance is sebetralstat.

The other ingredients are:

Tablet core: microcrystalline cellulose; croscarmellose sodium; povidone K30; magnesium stearate.

Film-coatings: Macrogol poly(vinyl alcohol) grafted copolymer; talc; titanium dioxide (E171); glycerol monocaprylocaprate (Type 1); poly(vinyl alcohol); iron oxide yellow (E172); iron oxide black (E172); maltodextrin; guar galactomannan; hypromellose; triglycerides, medium chain.

The contents of the pack

The tablets are packed in a blister encased in a child-resistant cardboard wallet. The wallets are contained in a cardboard box. The pack contains 4 or 6 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Sebetralstat

Chemical Names: IUPAC
N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide

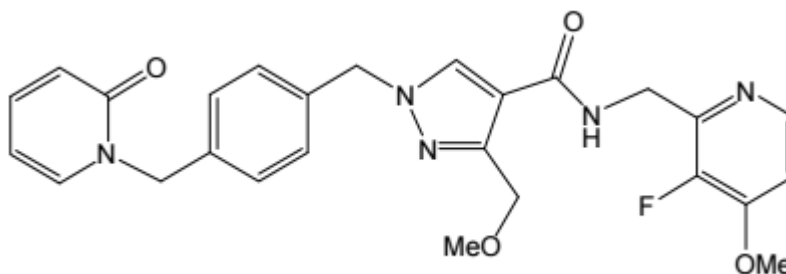
N-((3-fluoro-4-methoxypyridin-2-yl)methyl)-3-(methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide

Other name

N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-[[4-[(2-oxo-1,2-dihydropyridin-1-yl)methyl]phenyl]methyl]-1H-pyrazole-4-carboxamide

Molecular Formula: $C_{26}H_{26}FN_5O_4$

Chemical Structure:



Molecular Weight: 491.52

Appearance: White to off-white solid.
 Solubility:

Solvent	Solubility (mg/mL)	pH at Saturation
Deionised Water (measured pH 5.6)	0.05	5.7
Fasted-State Simulated Gastric Fluid (FaSSGF)	11	1.6
Citric Acid – Sodium Phosphate Buffer	0.4	3.0
Fed State Simulated Intestinal Fluid (FeSSIF)	0.08	5.0
Citric Acid – Sodium Phosphate Buffer	0.06	5.0
Fasted State Simulated Intestinal Fluid (FaSSIF)	0.1	6.5
Citric Acid – Sodium Phosphate Buffer	0.03	7.4
0.1M Hydrochloric Acid	33	Not determined
20% Vitamin E Polyethylene Glycol Succinate (aq) (20% TPGS)	3	Not determined
0.9% w/v NaCl	0.04	Not determined
Ethanol	4	Not determined
Ethyl Acetate	1	Not determined
Acetone	5	Not determined
Isopropanol	1.5	Not determined

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years without any special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

To support the clinical development and registration of sebetralstat for the intermittent, on-demand treatment of HAE, a comprehensive non-clinical package of in vitro and in vivo pharmacology, safety pharmacology, pharmacokinetics and drug metabolism, general toxicology, genetic toxicology, reproductive and developmental toxicology, carcinogenicity and phototoxicity studies have been conducted in accordance with the relevant International Council for Harmonisation (ICH) Guidelines and Good Laboratory Practice regulations, where applicable. The excipients used in the formulation for the intended Sebetralstat 300 mg Film-Coated Tablet formulation are conventional and the quantities are typically used in pharmaceuticals. Therefore, no specific toxicology studies on excipients were required.

All safety pharmacology and pivotal/definitive toxicity studies were carried out in full compliance with Good Laboratory Practice (GLP) regulations in a country that is a signatory of the OECD Mutual Acceptance of Data (MAD) programme. The toxicokinetics (TK) of sebetralstat in GLP-compliant toxicology and safety pharmacology studies were determined using validated bioanalytical assays.

Pharmacology studies have not been performed in compliance with GLP; however, they have been carried out in compliance with test facility standard operating procedures governing experimental activities. ADME studies were not performed in compliance with GLP; however, the practices and procedures during their conduct were consistent with GLP principles.

The human AUC and $C_{\max}$ data used for exposure ratio calculations were taken from a population PK modelling simulation (KV900-PPK1_SIM1 Report). Four dosing regimens (3 x 300 mg taken 0.75 hours, 3 hours and 8 hours apart, and 900 mg taken as a single dose) were simulated using population PK to determine which would be predicted to give the highest plasma exposure. Simulations were based on the demographics of subjects within KVD900-301 (excluding adolescents and those without a baseline weight). Each subject was randomly assigned inter-individual variation based on the distribution from the population pharmacokinetic (PK) model (CL, V2 and KA). A population of 500 subjects was simulated, and arithmetic mean PK parameters were calculated.

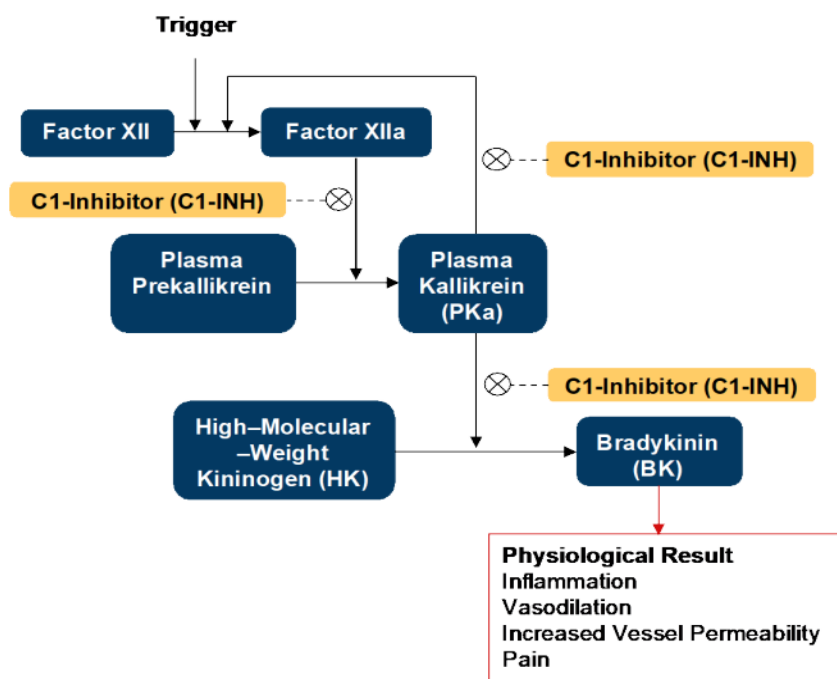
The highest mean $C_{\max}$ occurred after a single dose of 900 mg (i.e. where a subject took all three doses of 300 mg at the same time). This was calculated to be 8,580 ng/mL. The highest mean $AUC_{0-\infty}$ was similarly predicted to occur after a single dose of 900 mg; the same value (28,300 h*ng/mL) was also achieved when dosing 3 x 300 mg given 0.75 hours or 3 hours apart. Correction for the unbound fraction of sebetralstat in human plasma (0.232) results in an unbound plasma $C_{\max}$ of 1,991 ng/mL and an AUC of 6,566 h*ng/mL after a dose of 900 mg.

III.2 Pharmacology

Sebetralstat is a novel small molecule inhibitor of human plasma kallikrein (PKa) that has been developed as an orally administered tablet for the treatment of hereditary angioedema (HAE) attacks in adults and adolescents aged 12 years and older.

HAE is a rare, debilitating, and potentially life-threatening disease caused by insufficient activity of the complement component 1 inhibitor (C1-INH) regulating the kallikrein-kinin system (KKS) which results in spontaneous activation, leading to excessive PKa activity, cleavage of high molecular weight kininogen (HK), and increased production of bradykinin (BK). It is characterized by recurrent and often unpredictable tissue swelling due to an increase in vascular permeability and edema.

Plasma kallikrein is a serine protease integral to the contact activation pathway. It circulates in plasma as a zymogen, pre-kallikrein (PKK), bound to one of its main substrates, high-molecular-weight kininogen (HK). During contact activation, PKK is cleaved by activated factor XIIa forming the active protease kallikrein. Kallikrein in turn cleaves HK, producing bradykinin (BK). The activation of the BK B2 receptor by BK results in vasodilatation, increased vascular permeability, and smooth muscle contraction, leading to the tissue swelling that characterizes HAE, see figure below:

Figure 1: Activation of the Plasma Kallikrein-Kinin Enzymatic Pathway

The majority of cases of HAE are caused by mutations in SERPING 1, leading to an insufficiency of C1 esterase inhibitor (C1-INH), which is the major endogenous regulator of the contact activation pathway. This results in abnormally upregulated cleavage of HK by plasma kallikrein, releasing BK, which mediates angioedema.

Primary Pharmacology

Primary pharmacology was evaluated primarily by *in vitro* and *ex vivo* methods. Studies with isolated human PKa characterise sebetralstat as a competitive, reversible inhibitor human PKa. The inhibitory constant was 3.02 nM and association and dissociation constants indicate rapid association and dissociation from the active site (Studies 045_KV123900_PH_2016, 088_KV123900_PH_2018 and 089_KV123900_PH_2018).

Sebetralstat activity was also investigated by evaluating PKa enzyme activity and PKa substrate and cleavage product levels in human plasma from healthy subjects and HAE patients.

In plasma-based assays activation of the KKS was achieved by addition of activators to plasma. Both preincubation studies with sebetralstat and studies in which addition of sebetralstat occurred after activation of plasma were conducted.

In studies of activated human plasma from healthy subjects in which sebetralstat was added prior to addition of activator and a fluorogenic substrate the mean IC₅₀ was 54.0 nM. This increased value over the isolated enzyme assay was anticipated due to the greater concentration of PKa within the assay. Activity in *ex vivo* plasma of HAE patients was 47.5 nM (192_KVD900_PH_2021).

The above studies evaluated activity PKa after activation and prior incubation with sebetralstat. For the targeted indication sebetralstat would be administered after the initiation of an attack, not prior. A single *in vitro* study was conducted wherein sebetralstat was added after the activation of undiluted human plasma to mimic clinical use (146_KV123900_PH_2020). A rapid and

concentration-dependent inhibition of PKa enzyme activity was noted at concentrations of >300 nM.

The above assays measured fluorescence from an exogenous fluorogenic substrate, additional studies were conducted with immunoassay of endogenous substrates and cleavage products in undiluted human plasma. Sebetralstat was found to protect endogenous substrate HK from cleavage, protect further cleavage of precursor prekallikrein and reduce production of cleavage products cHK (a surrogate measure for BK) and Factor XIIa (Studies 115_KV123900_PH_2019 and 123_KV123900_PH_2019).

Similar studies were conducted *in vitro* and *ex vivo* for non-clinical species and confirmed the appropriate choice of rat and NHP as the non-clinical toxicological species, based on comparable inhibition in isolated enzyme assays and confirmed in *ex vivo* plasma-based assays in rat and NHP. The *ex vivo* studies also support that oral sebetralstat administration *in vivo* can result in decreased PKa enzyme activity (Studies 078_KV123900_PH_2017, 081_KV123900_PH_2017 and 083_KV123900_PH_2017). Activity was also confirmed for mouse PKa in an *in vitro* isolated enzyme assay, supporting suitability of this species in evaluation of carcinogenicity. However, sebetralstat did not inhibit cloned recombinant rabbit PKa enzyme, see table below:

Table 1: Sebetralstat Non-Human Plasma Kallikrein Enzyme Inhibition Data

	Mouse	Rat	Rabbit	Dog	Pig	NHP
PKa preparation	Commercially available recombinant mouse PKa enzyme	Isolated PKa from diluted Sprague Dawley rat plasma	Cloned recombinant rabbit PKa enzyme	Isolated PKa from diluted Beagle dog plasma	Isolated PKa from diluted Gottingen minipig plasma	Isolated PKa from diluted cynomolgus monkey plasma
Substrate	H-DPro-Phe-Arg-AFC	H-DPro-Phe-Arg-AFC	H-DPro-Phe-Arg-AFC	H-DPro-Phe-Arg-AFC	H-DPro-Phe-Arg-AFC	H-DPro-Phe-Arg-AFC
Type of assay	Ki	Ki	IC ₅₀	IC ₅₀	IC ₅₀	IC ₅₀
Result	K _i = 6.94 nM Competitive Inhibition	K _i = 37.15 nM Competitive Inhibition	IC ₅₀ = >40,000 nM	IC ₅₀ = 8,670 nM	IC ₅₀ = >40,000 nM	IC ₅₀ = 5.07 nM
Fold to Human Ki^a	2.3	12.3	>6,623	1,435	>6,623	0.8
Source	046_KV123900_PH_2016	047_KV123900_PH_2016	058_KV123900_PH_2016			

^a: Ki calculated value from IC₅₀ using Cheng Prusoff equation (058_KV123900_PH_2016), non-human PKa IC₅₀ assays were performed using the K_m concentration of substrate, thus the conversion from IC₅₀ to Ki is IC₅₀ ÷ 2

Rabbits were utilised as the second species for evaluation of embryofetal development and relevance of these findings to humans is uncertain.

No animal model of HAE was available at the time of development of sebetralstat. *In vivo* activity was studied instead in a general model of inflammation following injection of a recognised pro-inflammatory agent, the Carrageenan-Induced Paw Edema (CPE) model in rat. The model is recognised to include influence of bradykinin, amongst other mediators of inflammation. Oral pretreatment with sebetralstat reduced the carrageenan-induced response in this model (CPE-KPL-2). It is noted that pre-treatment with sebetralstat in this model does not mimic the clinical scenario where sebetralstat will be administered after the attack is recognised.

Secondary Pharmacology

The potential for interaction with secondary targets was evaluated *in vitro* using a panel of 14 serine proteases closely related to PKa as well as a wide-ranging commercially available panel of 124 receptors, enzyme, transporter and ion-channel binding targets, see table below:

Table 2: Secondary Pharmacology studies

Organ Systems Evaluated	Species/ Strain	Compound Administered	Method of Administration	GLP compliance	Test Site	Study Number
Off-target serine protease inhibition screening	Human	Sebetralstat	<i>In vitro</i>	No	KalVista Pharmaceuticals	057_KV123900_PH_2016
Off-target receptor, enzyme, and transporter interaction screening at a single 10 μ M concentration	Rat, rabbit, guinea pig, pig, bovine, human	Sebetralstat	<i>In vitro</i>	No	Eurofins, Taiwan	AB31416

Sebetralstat inhibited PKa binding but did not significantly inhibit binding at any other target. Selectivity for PKa over other serine proteases was >1,656 fold.

As plasma kallikrein is an upstream regulator of the coagulation pathway inhibition of PKa could be expected to inhibit production of Factor XIIa and impact its inhibition of the intrinsic coagulation cascade. While direct inhibition of serine proteases involved in the coagulation cascade (Factors VIIa, Xa, XIa, XIIa and thrombin) was not noted *in vitro*, coagulation parameters were monitored in toxicology (and clinical) programs. In toxicology studies, minimal increases in PT and aPPT of 1.3 and 1.6-fold, respectively, were observed for the high dose groups (≥ 300 mg/kg/day) in the 35-day repeat dose study in NHPs (8365930). A dose of 300 mg/kg resulted in exposures on day 1 of 4.1 and 2.5-fold compared to clinical exposure at the maximum recommended human dose (MRHD) based on unbound plasma AUC and C_{max} , respectively. No changes in these parameters were noted in longer term studies at lower doses. Clinical studies have not revealed any notable changes indicating an impact on coagulation.

Safety Pharmacology

A battery of safety pharmacology studies has been conducted in accordance with the guidelines in ICH S7A (Safety Pharmacology Studies for Human Pharmaceuticals) and ICH S7B (The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization [QT Interval Prolongation] By Human Pharmaceuticals). All pivotal studies were conducted to GLP. These studies are summarised in the table below.

Table 3: Safety Pharmacology Studies

Organ Systems Evaluated	Species/ Strain	Compound Administered	Method of Administration	Dose	Sex and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Cardiovascular system								
KVD900 effects on hERG tail current recorded from stably transfected Chinese hamster ovary cells	Human recombinant hERG channel	Sebetralstat in DMSO	<i>In vitro</i>	1.1, 3.3, 11 and 33 μ M	NA	At the highest concentration (33 μ M) sebetralstat blocked less than 35% hERG tail current. The IC_{50} is therefore >33 μ M	No	A1498
KVD900 effect on hERG tail current recorded from stably transfected HEK293 cells	Human recombinant hERG channel	Sebetralstat in DMSO	<i>In vitro</i>	3.0 and 30 μ M	NA	At the highest concentration (30 μ M) sebetralstat blocked less than 30% hERG tail current. The IC_{50} is therefore >30 μ M	Yes	A1711
KVD900 effects on cardiovascular system in the conscious telemetered NHP	NHP, cynomolgus monkey	Sebetralstat in 20% TPGS	Oral gavage	30, 100 or 300 mg/kg	Male 4/group	Sebetralstat had no effect on cardiovascular function, including ECG	Yes	8362593
Central nervous system								
KVD900 effects on general activity, behavior and body temperature	Rat, Han Wistar	Sebetralstat in 20% TPGS	Oral gavage	100, 350 or 1,000 mg/kg	Male 6/group	Sebetralstat did not induce behavioral, physiological, or body	Yes	8348817

Organ Systems Evaluated	Species/ Strain	Compound Administered	Method of Administration	Dose	Sex and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
(CNS/Irwin study) in the rat						temperature changes compared with controls		
Respiratory system								
KVD900 effects on respiratory parameters in the rat	Rat, Han Wistar	Sebetralstat in 20% TPGS	Oral gavage	100, 350 or 1,000 mg/kg	Male 6/group	Sebetralstat caused no biologically significant effects on respiratory parameters compared with controls	Yes	8348816

NA: not applicable

Non-clinical cardiovascular safety assessment consisted of evaluation of QT prolongation in the hERG K⁺ channel stably expressed in Chinese Hamster Ovary (CHO) cells (A1498) and human embryonic kidney (HEK293) cells (A1711), and a GLP compliant single dose in vivo cardiovascular safety pharmacology study in telemetered NHPs (8348816) which was supported by monitoring of cardiovascular endpoints in repeat dose toxicity studies in NHPs.

The two in vitro hERG study results were similar, with not more than 30% inhibition noted at the highest doses tested (30 and 33 μ M). Based on a human C_{max} for unbound sebetralstat of 4 μ M, there is a safety margin of >7.5 fold for the highest tested concentration in the hERG assay.

In the GLP compliant in vivo cardiovascular safety pharmacology study there was no sebetralstat related effect on any cardiovascular parameter measured at any dose and the NOAEL was determined to be the high dose, 300 mg/kg. The unbound plasma C_{max} exposure margin at the NOAEL of 300 mg/kg was 1.1x, compared to human exposure at the maximum recommended human dose (MRHD) of 900 mg (3 x 300 mg, unbound plasma C_{max} = 1,991 ng/ml). As a result of this low margin, reference is also made to the MTD and 7-day fixed dose toxicity study in NHPs (8359819) where larger unbound plasma C_{max} exposure margins of up to 6-fold were achieved, though there were limited number of animals included in this preliminary study. ECG was not monitored during this study, but no macroscopic or microscopic changes in cardiovascular tissue were noted. In pivotal 26-week intermittent-dose toxicity study in NHPs (20286942), no ECG changes were observed on days 89 and 180. At the high dose (300 mg/kg/dose) on day 176, mean unbound plasma C_{max} was 3,651 ng/mL, a margin of 1.8-fold over clinical exposure.

Clinical cardiovascular safety assessment (KVD900-109, thorough QT study) has been conducted and based on concentration-QTc analysis, an effect on QT can be excluded at up to sebetralstat plasma concentrations of ~16,900 ng/ml which is in excess of the maximal predicted C_{max} of 8580 ng/ml following a single 900 mg dose. No cardiovascular adverse events were noted in clinical studies. Please refer to Clinical Assessment Report for further detail.

There were no CNS or respiratory findings in rats given single doses of sebetralstat at dose levels up to 1,000 mg/kg/day in GLP compliant studies (8348817, 8348816), therefore there was no concern for clinical use in terms of these endpoints.

Unbound plasma exposure margins in pivotal safety pharmacology studies are given in **Table 9**.

Conclusion

The Applicant has demonstrated that sebetralstat is a competitive, reversible inhibitor of PKa in isolated enzyme studies. In addition, dose-dependent inhibition of PKa by sebetralstat as measured by an exogenous fluorogenic PKa substrate and by endogenous substrate and catalytic

products (increase in substrate HK and decrease in cleavage products cHK and Factor XIIa and increase in precursor PK) was observed in activated plasma assays. Studies have been conducted in plasma from both healthy volunteers and HAE patients with similar results. These studies support the utility of sebetralstat in the targeted indication.

A secondary pharmacology receptor screen and GLP compliant battery of safety pharmacology studies do not raise concerns.

The non-clinical species selected for general toxicology (rat and NHP) and carcinogenicity (mouse and rat) and reproductive toxicity (rat) studies showed comparable enzyme inhibition to that measured for the human enzyme. However, sebetralstat did not inhibit rabbit PKa, the second species utilised for evaluation of embryofetal developmental toxicity.

III.3 Pharmacokinetics

Validated analytical methods were used for analysis of mouse, rat, rabbit, dog and NHP plasma samples from GLP-compliant repeat dose toxicity, reproductive toxicity, and carcinogenicity studies. Validated analytical methods were used for analysis of dose formulations in pivotal studies. The methods, calibration ranges and corresponding validation reports are shown below:

Table 4: Summary of Methods of Analysis

Species/Sample Matrix	Analyte	Calibration Range	Method utilized	GLP Compliance (Y/N)	Study Number
Dose formulation	Sebetralstat	0.5-3 µg/mL 1.67-10 µg/mL	LC-UV	Y	8350958
Dose formulation	Sebetralstat	1.569-10 µg/mL	LC-UV	Y	JAM0008
Dose formulation	Sebetralstat	1.7-10 µg/mL	LC-UV	Y	JAM0016
Dose formulation	Sebetralstat	1.7-10 µg/mL	LC-UV	Y	JAM0017
Dose formulation	Sebetralstat	10-100 µg/mL	LC-UV	Y	8405179
Dose formulation	Sebetralstat	0.048-0.32 mg/mL	LC-UV	Y	20196163
Dose formulation	Sebetralstat	48-480 µg/mL	LC-UV	Y	20287544
Dose formulation	Sebetralstat	1.7-10 µg/mL	LC-UV	Y	JAM0044
Dose formulation	Sebetralstat	1.7-10 µg/mL	LC-UV	Y	JAM0045
Dose formulation	Sebetralstat	0.5-8 µg/mL	LC-UV	Y	20285216
Dose formulation	-	7.190-23.07 µg/mL	LC-UV	Y	JAM0093
Dose formulation	-	7.36-23.49 µg/mL	LC-UV	Y	JAM0097
Mouse plasma	Sebetralstat	10-10,000 ng/mL	LC-MS/MS	Y	01273002
Rat plasma	Sebetralstat	10-10,000 ng/mL	LC-MS/MS	N	8346068
Rat plasma	Sebetralstat	10-10,000 ng/mL	LC-MS/MS	N	8348811
Rat plasma	Sebetralstat	10-5,000 ng/mL	LC-MS/MS	Y	JAM0006
Rabbit plasma	Sebetralstat	10-5,000 ng/mL	LC-MS/MS	Y	JAM0007
Dog plasma	Sebetralstat	10-10,000 ng/mL	LC-MS/MS	N	8346069
Dog plasma	Sebetralstat	10-10,000 ng/mL	LC-MS/MS	N	8348810
NHP plasma	Sebetralstat	5.09-5,090 ng/mL	LC-MS/MS	N	8362393

NHP plasma	Sebetralstat	5-5,000 ng/mL	LC-MS/MS	N	8366594
NHP plasma	Sebetralstat	5-5,000 ng/mL	LC-MS/MS	Y	01273006

Bionalysis was performed using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and all assays used D₈-deuterated sebetralstat (KV126341) as the internal standard. Calibration ranges for all species were considered appropriate, with good definition of plasma concentration vs. time profiles, and without large numbers of samples requiring dilution into range.

All TK samples from GLP-compliant studies were analyzed within the validated frozen storage stability period. Incurred sample reanalysis was successfully demonstrated for all species and, as appropriate, where the assay was established at a different facility.

Pharmacokinetics has been evaluated in mice, rats, rabbits, dogs and NHPs. Rats and NHP were ultimately selected as the species used in the general toxicology studies, rats and rabbits in reproductive toxicity studies and mice and rats in the carcinogenicity studies.

Absorption

Sebetralstat was determined to be moderately permeable when evaluated in an *in vitro* study of intestinal permeability in 3-day human epithelial colorectal adenocarcinoma (Caco-2) cells at a concentration of 50 µM (051_KV123900_PK_2016).

PK studies, using LC-MS/MS to measure sebetralstat in plasma, were conducted in mice (068_KV123900_PK_2017), rats (067_KV123900_PK_2017), rabbits (108_KV123900_PK_2018), dogs (069_KV123900_PK_2017) and NHPs (070_KV123900_PK_2017, 086_KV123900_PK_2018, VNG6181_ZNA73779, 112_KV123900_PK_2018) using single i.v. and/or oral doses of [¹⁴C]sebetralstat. The formulations used in these PK studies were typically intended to enhance drug solubility and were not reflective of the clinical formulation. Orally administered sebetralstat was formulated as a liquid for oral gavage which is the method of administration in the pivotal toxicology studies, though various vehicles were used in PK studies. In the pivotal toxicology studies, sebetralstat was administered in 0.5% HPMC, which was included in some PK studies. In general, while there is variability in absorption, depending on the vehicle, values were broadly comparable. Solid formulations were administered to NHPs in some PK studies; however, toxicology studies used oral gavage administration and these are not considered relevant.

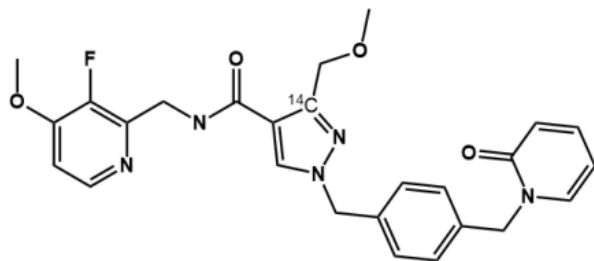
After a single oral administration, sebetralstat absorption was relatively rapid, with T_{max} generally observed less than or approximately 1 hour post administration, though this was variable depending on formulation and generally increased with increasing dose. Oral bioavailability relative to i.v. administration ranged from 27 to 29% in mice, 23 to 167% in rats, 34% in dogs and 22 to 48% in NHPs. Variability was noted depending on formulation and on dose.

Clearance was moderate and volume of distribution low (generally <0.8 L/kg and consistent with volume of body water) in rodents and dogs. In NHPs, clearance and volume of distribution was higher. Clearance was ~75% of liver blood flow and volume of distribution 1.5 L/kg corresponding to ~twice the volume of body water.

Plasma half-life was short across non-clinical species, being generally ≤ 1 hr after i.v. administration. In NHPs administered oral sebetralstat at approximately 34 mg/kg (in 3 different vehicles), half-life ranged from 1.8 to 2.4 hours.

A comprehensive ADME profile of sebetralstat was determined after oral administration of [^{14}C]sebetralstat in rats and non-human primates (NHP; cynomolgus monkeys), the rodent and non-rodent toxicology species. The site of labelling is shown below:

Figure 2: Sebetralstat site of labelling



After dosing [^{14}C]sebetralstat orally to rats (181649) and NHPs (182658), liquid scintillation counting (LSC) was used to measure radioactivity in plasma and blood samples. In these studies, [^{14}C]sebetralstat was formulated in 0.5% HPMC in water, the same formulation used in 13- and 26-week toxicology studies. In rats and NHPs drug-related material was rapidly absorbed in both sexes. In rats, the AUC of total radioactivity and, to a lesser extent the C_{max} , was higher in female rats than in males. Blood levels of total radioactivity were lower than those in plasma, with the exception of the 24 hour sample in male rats where levels were slightly higher in blood. In NHPs the AUC of total radioactivity was broadly similar between sexes. The exposure of total radioactivity in blood was slightly lower than that in plasma.

PK of repeat dosing was evaluated as part of the toxicity studies in mice, rats, pregnant rats, pregnant rabbits, dogs and NHPs. Similarly to single-dose studies, the absorption of sebetralstat was generally rapid, with T_{max} typically being between 0.25-1 hour in mice, 0.5-4 hours in rats, 1-2 hours in dogs and 1-2 hours in NHPs. Plasma exposure was demonstrated in all studies, with exposure increasing with dose; C_{max} typically increased in proportion to dose, whereas AUC was generally supra-proportional or proportional to dose. In rodents, females typically had higher exposure than males upon single dosing, but higher accumulation was observed in males such that exposures were similar between sexes upon repeated dosing. It is not clear how accumulation is occurring in male rats given the short plasma half-life of sebetralstat. No consistent sex difference in TK was seen in dog or NHP and accumulation upon repeat dosing in NHPs was typically not observed. Based on percentage of radioactivity in faeces of bile-duct cannulated rats and percent unchanged sebetralstat in faeces of NHPs, it was estimated that 70 to 80% of an oral dose was absorbed.

Distribution

In vitro plasma protein binding (5 μM) was higher in rodents (94.1% and 96.1% in mouse and rat, respectively) and more moderate in other species; 87.5% in rabbit, 65.9% in dogs, 62.4% in NHPs and 76.8% in humans (049_KV123900_PK_2016).

In vitro red blood cell to plasma partitioning was estimated in mouse, rat, dog, pig, NHP and human blood. Mean blood to plasma ratios were 0.60, 0.56, 0.80, 0.93, 0.90 and 0.80, respectively, indicating limited partitioning of sebetralstat into red blood cells (YDS/060).

Tissue distribution was investigated in albino male HW rats, in Lister Hooded pigmented male rats and in time-mated albino HW female rats (GD 16) following oral dosing of 30 mg/kg [^{14}C]sebetralstat (181649). Radioactivity was widely distributed to all tissues, with T_{max} in the majority of tissues observed at 0.5 or 1 hour post-dose. Concentrations decreased markedly at 4 and 8 hours post-dose and were not distinguishable or below the limit of reliable measurement in the majority of tissues after this time. With the exception of liver, kidney and adrenal gland, radioactivity was not quantifiable in tissues by 72 hours post-dose. Overall, highest concentrations of radioactivity were associated with excretory organs (liver, kidney, stomach wall, small and large intestinal wall) and adrenals. There was limited penetration into brain and spinal cord and testes.

In time-mated females, maternal distribution was similar to that observed in male albino rats, with highest concentrations of radioactivity in the liver and kidneys. The concentration of radioactivity in the whole fetus was only measurable at 1 hour post-dose. Similarly, in a study utilising a higher dose level administered orally on Day 16 of gestation, the concentration of radioactivity in fetus at 1 hour after the maternal dose was low compared to maternal blood and plasma concentrations (187593). Ratios of total radioactivity for fetus:whole blood and fetus:plasma were 0.08 and 0.05, respectively.

Following oral administration to male pigmented rats, radioactivity was not detectable in the majority of tissues at 24 hours post-dose, the first sampling time. Radioactivity was measurable at low levels in liver and kidney, with concentrations decreasing over the course of the study period. In addition, radioactivity was present in melanin containing tissues (pigmented skin and eye) in pigmented male rats at higher levels than in albino animals and was observed at later timepoints. No radioactivity was observed in albino or pigmented skin at the 168hr time point. While no radioactivity was noted in the eye of albino rats by 24 hours, in the eye of pigmented rats, radioactivity associated with the uveal tract was measurable at 336 hours though this was decreased from previous time points indicating dissociation. Limited melanin binding was observed in vitro (053_KV123900_PK_2016).

Metabolism

In vitro metabolism in liver microsomes and hepatocytes were conducted to evaluate intrinsic clearance of sebetralstat (048_KV123900_PK_2016, 2015_09_15_Kalvista_WO) and to compare metabolic profiles in different species (ADM-16-1410, ADM 17 1731). In all species, extensive metabolism was observed. All metabolites generated by human hepatocytes were also formed by hepatocytes from rat and NHP, supporting the suitability of these species for the repeat-dose toxicity studies.

In vivo studies also indicate extensive biotransformation. Initial *in vivo* metabolite profiling in human, rat and NHP plasma was undertaken by LC-MS/MS (YDS/082). Metabolites in human plasma were characterised at 1 and 8 hours after a single dose of 600 mg/kg and for rats and NHPs after 7 days repeated dosing at 300 mg/kg/day and 100 mg/kg/day, respectively. 14 metabolites were detected in human plasma, all of which were also observed in rat and NHP plasma. Human metabolites were formed from oxidation, di-oxidation/di-hydrogenation, O-demethylation, O-demethylation/oxidation, oxidation/glucuronidation, oxidative N-dealkylation, and di-oxidation/methylation. All metabolites present in human plasma were also present at

similar or higher levels in a matrix-matched comparison of time-normalised AUC₀₋₂₄ pools from NHPs. In rats, all metabolites were present; however, 4 were noted at lower levels than in human plasma.

Metabolite M19 was subsequently identified as the most abundant plasma metabolite in humans. This metabolite was not identified in plasma of rats in the LC-MS/MS metabolic profiling study, though it was subsequently quantified (8457943, 8463718) in plasma from rats in the 26-week repeat dose toxicity study. In NHPs, M19 co-eluted with M3 but was subsequently quantified (8457942, 8463724) in plasma from NHPs in the 13-week intermittent dosing toxicology study.

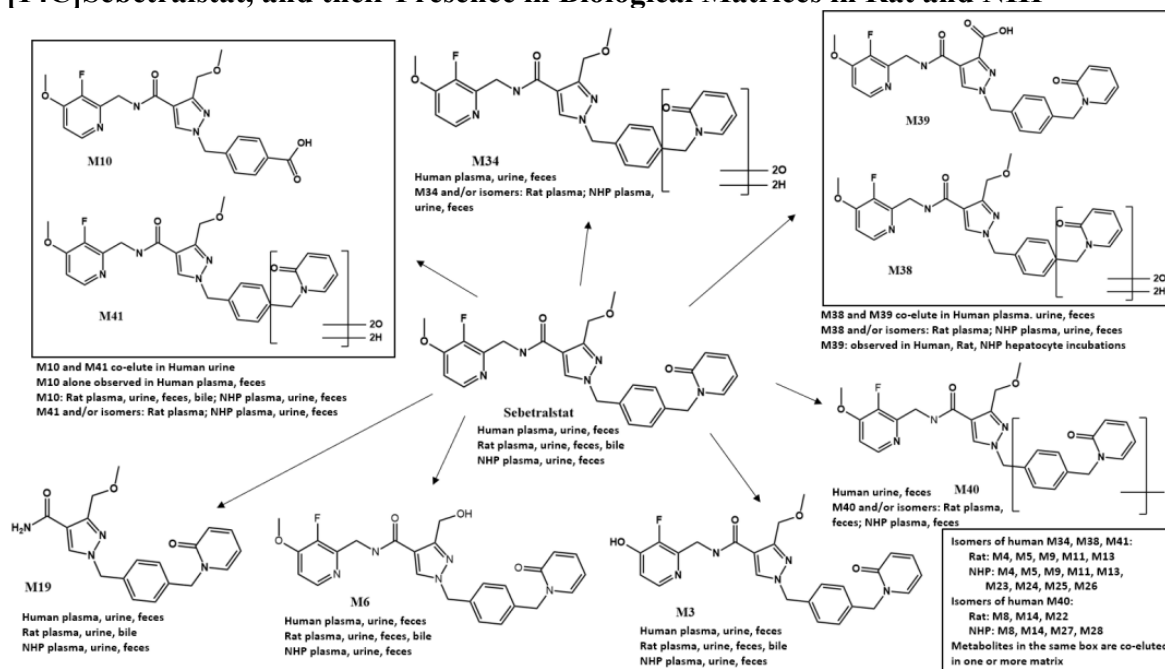
Definitive metabolic profiles in plasma, urine, faeces and bile (rats only) were determined after dosing of radiolabelled sebetralstat in rats and NHPs and compared with humans. In humans, after dosing 600 mg of [¹⁴C]sebetralstat orally, sebetralstat was the predominant component in plasma (KVD900-103). No metabolite accounted for a mean of >10% of drug-related material in the AUC₀₋₂₄ across subjects. The most abundant plasma metabolites were the cleavage products M19 and M10 (mean of 7.10% and 4.00% of AUC₀₋₂₄ respectively) and the pyridyl desmethyl product M3 (mean of 4.01% of AUC₀₋₂₄). There was extensive biotransformation to a variety of metabolites, but sebetralstat was the main drug-related component in urine and faeces (mean of 8.66% and 12.5%, respectively across subjects). No subject excreted more than 13% of the dose as sebetralstat in urine. The main routes of biotransformation, represented by those metabolites which formed >5% of the dose in excreta, were via chain cleavage at two different points in the molecule (M19 and M10; M10 co-eluted in urine with a di-oxidation/di-hydrogenation product, M41), a di-oxidation/di-hydrogenation product (M34) and the pyridyl desmethyl product M3. The most predominant metabolites excreted were M34 and M3 (11.3% and 10.7% of the dose, respectively).

In rats dosed with [¹⁴C]sebetralstat, there was extensive biotransformation of parent compound (181649). The amount of parent eliminated unchanged was difficult to assess due to co-elution with other metabolites but represented <4% of dose in urine and was the major circulating component in plasma. Identified metabolites included O-demethylation, hydroxylation, and products of cleavage of sebetralstat.

In NHP, there was likewise extensive biotransformation of [¹⁴C]sebetralstat (182658). Sebetralstat represented <0.5% dose in urine and ≤20% in faeces. Identified metabolites included O-demethylation, hydroxylation, di-oxidation/di-hydrogenation, and cleavage products of sebetralstat. In NHP plasma AUC pools, parent compound was the major drug-related component, but a hydroxy glucuronide was almost equally prevalent, along with a number of other metabolites whose individual quantification was not possible due to co-elution, including the cleavage products M19 and M10 and the pyridyl desmethyl product M3.

The most abundant human plasma and excreta metabolites are shown below, along with the presence of these components (and/or their isomers) in biological matrices from rat and NHP.

Figure 3: Major Metabolites (>2% of Dose Excreted of >2% of AUC0-24 of Plasma Total Radioactivity) Detected in Human Urine, Faeces and Plasma after Oral Dosing of [14C]Sebetralstat, and their Presence in Biological Matrices in Rat and NHP



The CYP isoforms responsible for metabolism of sebetralstat were investigated in human liver microsomes in two *in vitro* studies. An initial screening study indicated metabolism by a range of CYP isoforms, with the largest contribution from CYP3A4 (YDS058). A further study, with optimized incubation conditions and radiolabelled sebetralstat, confirmed that CYP3A4 was responsible for the majority of sebetralstat metabolism, albeit to a higher extent than suggested by the initial study, with a minor contribution from CYP2C8 (181764).

Excretion

Following administration of radiolabelled sebetralstat orally to rats (181649) and NHPs (182658), recovery was high and radiation predominantly associated with the faeces (91% of total 99% recovered in rats and 82% of 95% recovered in NHPs). Just 7% and 10% of the dose was recovered in urine in rats and NHPs, respectively. In the urine of rats and NHPs, most sebetralstat related material was determined to be metabolites. In bile duct cannulated rats, 55.1% of radioactivity was recovered in bile mostly as sebetralstat metabolites. Metabolism is therefore considered the main route of elimination for sebetralstat.

In humans, after a dose of 600 mg radiolabelled sebetralstat to healthy male subjects, approximately 32% of radioactivity was excreted in urine and 63% was excreted in faeces (KVD900-103).

Excretion of sebetralstat occurs in the milk of lactating female rats (187593). Sebetralstat associated radioactivity was present at slightly higher levels than those present in plasma indicating that pups will be exposed to sebetralstat related material prior to weaning in the PPND study.

PK Interactions

Several *in vitro* studies were performed to investigate the potential for sebetralstat to cause, or to be a victim of, PK drug interactions. These were carried out with reference to appropriate regulatory guidelines (FDA, 2020; EMA, 2012).

Two studies investigated the inhibitory effect of sebetralstat on the activities of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 (CYP0603_R7, 182574). The second study was carried out at higher concentrations of sebetralstat based on observed clinical plasma concentrations. Sebetralstat caused <50% inhibition of CYPs 1A2, 2B6, 2C8, 2C19 and 2D6 up to a concentration of 200 µM and direct inhibition of CYPs 2C9 and 3A4 with IC₅₀s of 30.1 µM (CYP2C9), 120 µM (CYP3A4 testosterone substrate) and 121 µM (CYP3A4, midazolam substrate). No time-dependent inhibition of any CYP isoform was observed.

The ability of sebetralstat to cause inhibition of six major uridine 5'-diphospho-glucosyl transferase (UGT) isoforms was determined (CYP0603_R7). Sebetralstat was found to be a weak inhibitor of UGT1A1, UGT1A3, UGT1A4 and UGT1A9, but did not inhibit UGT1A6 or UGT2B7.

The potential for sebetralstat to be an inducer of CYPs 1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 was assessed by measuring its effect on levels of mRNA in incubations of cultured human hepatocytes from three donors (181759). No evident induction of CYP1A2 was observed. Induction of CYP2B6 was evident in cells from two donors at a sebetralstat concentration of 100 µM; however, the induction was <25% of that elicited by the positive control. Induction of CYP2C8 was evident in cells from all three donors at 100 µM sebetralstat. Apparent induction of CYP2C9 and CYP2C19 was evident in cells from two and one donors, respectively at 100 µM sebetralstat; however, interpretation of the extent of induction was difficult due to the low induction shown by the positive control. Induction of CYP3A4 was observed in cells from all donors at 100 µM sebetralstat and, to a lower extent and with variability between donors, at 10 µM sebetralstat.

The potential of sebetralstat to inhibit human solute carrier (SLC) transporters, the ATP-binding cassette (ABC) transporters BCRP and P-gp, and the bile salt export pump (BSEP) was studied *in vitro*. Sebetralstat caused inhibition of all SLC transporters, apart from OAT1 (KVS/REP/20). Sebetralstat caused no dose-dependent inhibition of P-gp, but weak inhibition of BCRP and BSEP (KVS/REP/22).

Investigations were performed to assess whether sebetralstat was a substrate of P-gp and BCRP (KVS/REP/23), or of any SLC transporters (KVS/REP/21). Sebetralstat was not a substrate of SLC transporters, with the exception of it being a borderline substrate of MATE2-K. Sebetralstat was found to be a substrate of both BCRP and P-gp.

The Applicant asserts that given that sebetralstat is intended as an intermittent (on-demand) treatment, where plasma concentrations rapidly decrease following an early T_{max} it is considered that the potential impact of sebetralstat as a perpetrator of CYP- and transporter-mediated drug-drug interactions is low. Further discussion of PK interactions is included in the Clinical Pharmacology Assessment.

Conclusion

Overall, the PK of sebetralstat has been adequately characterised in non-clinical species and interspecies comparisons support the selection of rat and NHP as the general toxicity species.

III.4 Toxicology

All pivotal non-clinical studies (studies identified in International Council for Harmonisation (ICH) guidelines as being required to support global regulatory authority submissions), were conducted in accordance with Good Laboratory Practice (GLP) and performed in a country that is a member of the Organization for Economic Co-operation and Development (OECD) Mutual Acceptance of Data program, in accordance with the OECD Test Guidelines and principles of GLP.

Initial toxicology studies were conducted using 20% D- α -tocopherol polyethylene glycol 1,000 succinate (TPGS) as the vehicle for sebetralstat dosing formulations. A change of vehicle to 0.5% hydroxypropylmethylcellulose (HPMC) was subsequently instigated as background control data for this vehicle was more extensive than that available for TPGS, particularly for longer term non-clinical studies. Bridging studies to support the change of vehicle were conducted in rats, rabbits, and NHPs. Data from these studies supported the change in formulation, which was implemented after the 28-/35-day repeat dose toxicology studies and before the conduct of the pivotal reproductive toxicology studies.

To support clinical development of sebetralstat, the sponsor conducted a package of *in vivo* repeat dose toxicology studies in rats (Crl:WI(Han)), dogs (Beagles) and the NHP (*Cynomolgus* monkeys; *Macaca fascicularis*, of Mauritian origin). Reversibility was examined in rat studies of up to 13 weeks duration and in all repeat dose studies in NHPs. Intermittent (twice weekly) dosing in the 13- and 26-week studies in NHP's was agreed by the FDA and is consistent with the intended pattern of intermittent (on-demand) clinical dosing.

Stand-alone single dose studies were not conducted as single dose toxicity was effectively evaluated during the maximum tolerated dose (MTD), acute 3-day administration studies (ICH M3 (R2)).

The use of rats as the appropriate rodent non-clinical toxicological species to study sebetralstat was justified by the sequence homology (approximately 75%) of PKa between rat and human, by a comparable inhibition of PKa by sebetralstat *in vitro* in rats and humans, and by a qualitatively similar pattern of metabolites.

Initially, dogs were selected as the non-rodent species to assess the potential toxicological effects of sebetralstat. However, in a 28-day repeat dose toxicology study, sebetralstat produced severe local tolerance effects in the gastrointestinal tract at a dose level of 100 mg/kg/day. Dogs were therefore considered not appropriate for further toxicological investigations. Subsequently, the NHP was selected as the non-rodent species for characterizing the toxicology of sebetralstat. Selection of the NHP was further supported by the fact that the sequence homology of PKa between humans and NHP is 90% or greater and sebetralstat is a more potent inhibitor of NHP PKa ($IC_{50} \cong 5$ nM) than of dog PKa ($IC_{50} > 8,000$ nM) *in vitro*. Furthermore, the metabolic profile of sebetralstat is qualitatively similar between humans and NHPs *in vitro*.

An *in vitro* bacterial mutagenicity assay (Ames), and an *in vitro* mouse lymphoma assay (MLA) have been conducted, and an *in vivo* micronucleus assay was undertaken as part of the 28-day repeat dose study in rats.

The potential for carcinogenicity has been examined in a pivotal 26-week repeat dose study in the CbyB6F1/Tg(HRAS)2Jic transgenic mouse, an a pivotal 104-week repeat dose study in rats. A

10-day and a 28-day dose ranging study in Wild Type CbyB6F1/Tg(HRAS)2Jic mice was conducted to enable dose level selection for the pivotal mouse study.

A fertility and early embryonic development study and pre-and post-natal development study was conducted in rats, and dose range finding, and pivotal embryo-fetal development (EFD) studies were conducted in rats and rabbits. A preliminary non-GLP study in juvenile rats has also been conducted.

The plasma toxicokinetics (TK) of sebetralstat were characterized using validated, specific bioanalytical methods in the general repeat dose toxicology studies in rats, dogs and NHPs, in EFD and fertility studies in rat and/or rabbit, in the pilot juvenile toxicity study in rat, and in the dose-range finding and the pivotal carcinogenicity studies in mouse and rat.

Sebetralstat absorbs light within the natural light range (290-700 nm), the highest absorbance being observed at 303 nm. Phototoxicity was evaluated in a Reactive Oxygen Species (ROS) and in an *in vitro* phototoxicity assay in 3T3 cells.

In addition, an *in vitro* bacterial reverse mutation assay and *in vitro* micronucleus assay was conducted for two impurities that were identified as requiring further qualification.

General Toxicology

The non-clinical toxicological profile for sebetralstat was characterised in rats and cynomolgus monkeys, which have been demonstrated to be relevant species based on pharmacological response and similarities in metabolism. The route of administration for these studies was oral gavage which is appropriate for the intended clinical use.

GLP compliant repeat-dose toxicity studies were conducted in HW rats and Cynomolgus monkeys.

Repeat Dose studies are summarised in **Table 5**.

Table 5: Summary of Repeat-Dose Toxicity Studies

Type of Study	Species, Strain	Duration of Dosing	Route of Administration/ Dose ^a	Compound Administered	NOAEL mg/kg/day(dose)	GLP Compliance	Report/ Study Number
Maximum tolerated dose (MTD) followed by a 7-day fixed dose (FD) phase toxicity study	Rat, Crl:WI(Han)	3 days (MTD), 7 days (FD)	Oral 25, 100, 250, 1,000 mg/kg/day in MTD phase Oral 0, 350 and 1,000 mg/kg/day in FD phase	Sebetralstat in 20% TPGS	1,000	No	8336506
7-day toxicity bridging study	Rat, Crl:WI(Han)	7 days	Oral 100, 300 mg/kg/day	Sebetralstat in 0.5% HPMC	300	Yes	8391045
28-day toxicity study followed by a 4-week recovery period	Rat, Crl:WI(Han)	28 or 29 days	Oral 0, 30, 100, 300, 1,000 mg/kg/day	Sebetralstat in 20% TPGS	300	Yes	8348815
13-week toxicity study followed by a 4-week recovery period	Rat, Crl:WI(Han)	13 weeks	Oral 0, 30, 100, 300 mg/kg/day	Sebetralstat in 0.5% HPMC	300	Yes	8401650
26-week toxicity study	Rat, Crl:WI(Han)	26 weeks	Oral 0, 30, 100, 300 mg/kg/day	Sebetralstat in 0.5% HPMC	300	Yes	8418576

Type of Study	Species, Strain	Duration of Dosing	Route of Administration/ Dose ^a	Compound Administered	NOAEL mg/kg/day(dose)	GLP Compliance	Report/ Study Number
MTD followed by a 7-day FD toxicity study	Dog, Beagle	3 days (MTD), 7 days (FD)	Oral 25, 100, 250, 1,000 mg/kg/day in MTD phase Oral 100 to 1,000 mg/kg/day initially, followed by 0, 100, 200, 300 mg/kg/day in FD phase	Sebetralstat in 20% TPGS	100	No	8338854
28-day toxicity study followed by a 4-week recovery period	Dog, Beagle	28 or 29 days	Oral 0, 25, 50, 100 mg/kg/day	Sebetralstat in 20% TPGS	50	Yes	8348814
MTD followed by a 7-day FD toxicity study	NHP, cynomolgus monkey ^b	3 days (MTD), 7 days (FD)	Oral 25, 100, 250, 500, 1,000 mg/kg/day in MTD phase Oral 0, 100, 300, 1,000 mg/kg/day in FD phase	Sebetralstat in 20% TPGS	100	No	8359719
7-day toxicity bridging study	NHP, cynomolgus monkey	7 days	Oral 50, 100 mg/kg/day	Sebetralstat in 0.5% HPMC	100	Yes	8391044
35-day toxicity study followed by a 4-week recovery period	NHP, cynomolgus monkey	35 days	Oral 0, 50, 100, 300, 500/300 ^c mg/kg/day	Sebetralstat in 20% TPGS	50	Yes	8365930
13-week toxicity study with a 4-week recovery period	NHP, cynomolgus monkey	13 weeks	Oral 0, 10, 25, 50 mg/kg/day	Sebetralstat in 0.5% HPMC	50	Yes	8382423
13-week intermittent toxicity study with a 4-week recovery phase	NHP, cynomolgus monkey	13 weeks	Oral twice weekly 0, 50, 100, 200, 300 mg/kg/dose (Monday & Friday)	Sebetralstat in 0.5% HPMC	300	Yes	8420897
26-week intermittent toxicity study with an 8-week recovery period	NHP, cynomolgus monkey	26 weeks	Oral twice weekly 0, 15, 50, 150, 300 mg/kg/dose (Monday & Friday)	Sebetralstat in 0.5% HPMC	300	Yes	20286942

Rats:

Repeated dose toxicity studies conducted in rats indicate that sebetralstat administered orally for up to 26 weeks, up to 300 mg/kg/day was well tolerated (Study Numbers: 8336506, 8391045, 8348815, 8401650, 8418576). Clinical observations were limited to salivation and mouth rubbing. Haematological changes were consistent through studies and include increased reticulocytes, red cell distribution width and haemoglobin distribution width and low haemoglobin which could be indicative of increased erythrocyte turnover. In a 28-day study spleen weight was increased and haemopoiesis in the spleen was observed on microscopic evaluation, particularly at 1000 mg/kg/day (8348815). However, in the 13 and 26 week studies the haematology findings were not accompanied by changes in the spleen weights or histopathological correlates and given the minimal severity, these changes are not considered adverse (8401650, 8418576).

Target organs of toxicity were liver, kidneys, adrenals, ovary and thyroid but the severity of the changes were minimal and there was evidence of complete, or partial reversibility when recovery was assessed after 4 weeks (28-day study 8348815; 13 week study; 8401650).

Increased liver weight and microscopic liver findings of centrilobular hepatocyte hypertrophy were seen in all rat studies. A few incidences of increases in mitotic figures and periportal vacuolation were apparent only at 1,000 mg/kg/day in the 28-day study (8348815). Pathological findings indicative of degeneration in the liver were absent and clinical pathology markers indicating liver dysfunction were not observed except for low total protein and consistently high cholesterol. The degree of biomarker elevation was maximal at 2.2-fold at doses of ≥ 300 mg/kg/day in the shorter duration (28 day) study but was 1.6-fold at 300 mg/kg/day in the 26-week study (8418576). High cholesterol was noted to be elevated by 1.4 fold in both sexes at 300 mg/kg/day in the 13-week study which also evaluated reversibility (8401650). In this study low total protein and albumin in females were observed in females in all dose groups. Cholesterol and protein were not elevated in recovery animals. Overall, liver changes in rats were considered to be an adaptive response and not considered adverse.

Findings in the kidneys include reduced accumulation of hyaline droplets, a finding observed in male rats which lacks clinical relevance. In addition, in the 26-week study, high dose females had increased unadjusted kidney weight and kidney:body weight and kidney:brain ratios, generally correlating with minimal to slight tubule cell hypertrophy (8418576). In-life findings included increased water consumption, increased urine volume. These findings were considered minimal and not adverse; however, they were not noted in the shorter duration 13-week study and therefore whether these histopathological changes are reversible is not known. The corresponding clinical chemistry and urinalysis parameters were comparable with controls at the end of the recovery period .

A number of endocrine functional organs (adrenals, ovary and thyroid) were affected in the rat studies (8391045, 8348815, 8401650, 8418576). These were evaluated and considered by the applicant to be secondary to adaptive responses, non-adverse and lacking clinical relevance. In the adrenal cortex, cortical hypertrophy or vacuolation was observed accompanied by an increase in weight. This was attributed to a stress response, which is possible, though it was not accompanied by a stress leukogram or lymphoid atrophy in the thymus and was not confirmed by measurement of glucocorticoids. However, there were no degenerative lesions noted and a trend toward reversibility observed at the end of the recovery period in the 13-week study. It is noted that high cholesterol is consistently observed following sebetralstat administration which may also be an effect of stress.

Ovarian interstitial cell hypertrophy was consistently observed at the dose level of 300 mg/kg/day and graded as minimal to slight. In the 28-day study at 1000 mg/kg/day additional findings of hypertrophy of corpora luteum and abnormal dioestrus were observed, but these findings were absent in the longer duration studies at lower doses. This is attributed to a secondary effect of an adaptive response in steroid synthesis. Incidence and severity of ovarian findings was reduced in recovery animals 4 weeks after dosing cessation indicating partial reversibility. No obvious functional effects were noted in the Fertility and Early Embryonic Development study in rats.

The increase in severity and incidence of thyroid follicular cell hypertrophy in rats in most studies and increase in thyroid weight in all studies was considered secondary to the liver enlargement observed. The hypertrophic response resulting from the increased thyroid metabolism. The applicant states that rats are particularly sensitive to this effect given they lack

thyroid binding globulin in plasma; however, thyroid hormone concentrations were not measured as confirmation. No increase in thyroid weight was noted at recovery in the 13 week period indicating reversibility, though that in this particular study histopathological changes in the thyroid were not observed and recovery was not examined in the 26-week study.

Due to non-adversity of findings in the high dose group in the chronic studies, the NOAEL is the high dose group, 300 mg/kg/day. In the 26-week rat study, this corresponds to a margin of safety to the maximum clinical dose (3 x 300 mg) of 5.8-fold for unbound plasma AUC (as calculated by the Applicant based on comparison to clinically predicted AUC_{0-inf}) and 1.9-fold for unbound plasma C_{max}.

Non-human Primates:

Studies in NHPs administered oral sebetralstat daily were conducted for up to 13 weeks in duration (8359719, 8391044, 8365930, 8382423). The liver was identified as the target organ of toxicity. Daily administration of sebetralstat induced hepatotoxicity at doses ≥ 300 mg/kg/day in the 35-day study (8365930). Declining clinical condition was noted in NHPs administered ≥ 300 mg/kg/day (500/300 and 300 mg/kg) daily and three animals were terminated prematurely on day 16, and 29. The remaining animals in these dose groups were also terminated early (day 30) due to poor condition.

The cause of the moribund condition was determined to be hepatotoxicity. Daily doses of ≥ 300 mg/kg/day were associated with histopathological changes in the liver including hepatocyte hypertrophy, necrosis, bile duct hyperplasia, inflammatory cell infiltration and Kupffer cell and hepatocyte pigmentation. These findings correlated with increased liver enzymes, notably ALT and GLDH. Non adverse liver pathology was observed at 100 mg/kg/day but reduced body weight and poor condition resulted in a NOAEL of 50 mg/kg/day.

Liver findings consisting of elevated liver enzymes (ALT and GLDH) and increased mononuclear cell infiltrates, with a few instances of hepatocellular necrosis/degeneration and Kupffer cell pigmentation were noted in the 13-week daily administration of up to 50 mg/kg/day (8382423). There was no good correlation between clinical pathology findings and histopathology findings and no clear dose response. In addition, some control animals were affected. This resulted in no NOAEL being assigned for this study. Following a Pathology Working Group peer review (see EPL Project No.: C77-002), these findings were considered a background finding which was marginally exacerbated by sebetralstat and the high dose of 50 mg/kg/day was subsequently determined to be the NOAEL based on non-adversity of these findings (8382423).

Subsequent studies (8420897, 20286942) utilised twice weekly oral dosing which is more reflective of the clinical scenario for an on-demand treatment for HAE attacks. This also allowed for higher doses to be administered.

Liver pathology findings were observed in the 13-week intermittent dosing study (8420897); however, there was no dose-response effect and control animals were also affected. Clinical chemistry abnormalities (raised ALT, GLDH and/or AST) were noted in some animals, including controls. No dose, exposure or time-response relationship was apparent. Subsequent analysis of liver samples indicated Hepatitis A infection in 20 of 42 animals on the study. Re-examination in light of these findings indicated HAV infection to be associated with liver findings. In the pivotal 26-week study, where NHPs were vaccinated against HAV, sebetralstat was well tolerated at the

high dose of 300 mg/kg twice weekly (20286942). No evidence of sebetralstat liver toxicity was observed.

Of note, the minimally prolonged clotting parameters in the 35-day study at doses of ≥ 300 mg/kg, were not observed at lower doses administered for longer duration (up to 50 mg/kg/day) daily or doses of 300 mg/kg administered intermittently (twice weekly).

Exposures in the 26-week intermittent dosing study at the NOAEL of 300 mg/kg (highest dose tested) resulted in margin of safety to the maximum clinical dose (3 x 300 mg) of 2.4-fold for unbound AUC (as calculated by the Applicant based on comparison to clinically predicted AUC_{0-inf}) and 1.8-fold for unbound plasma C_{max}.

Genotoxicity

Sebetralstat has been tested in a standard battery of GLP compliant genotoxicity studies in accordance with ICH guidance. Results of these studies were negative and sebetralstat is not considered to pose a genotoxicity hazard.

The following Genotoxicity studies were conducted:

Table 6: Summary of Genotoxicity Studies Conducted

Type of Study	Species, Strain	Duration of Dosing	Route of Administration/ Dose ^a	Compound Administered	GLP Compliance	Report/ Study Number
<i>In vitro</i> - screening Ames test	-	-	Concentration range 4,883-5,000 mg/mL	Sebetralstat in DMSO (up to 5% final)	No	8336497
<i>In vitro</i> - Ames test	-	-	Concentration range 5-5,000 mg/plate	Sebetralstat in DMSO (up to 5% final)	Yes	8348812
<i>In vitro</i> - Mouse lymphoma assay	-	-	Concentration range 50-492 mg/mL	Sebetralstat in DMSO (up to 1% final)	Yes	8348813
<i>In vivo</i> – micronucleus	Rat, Crl:WI(Han)	28 days*	Oral 0, 30, 100, 300, 1,000 mg/kg/day	Sebetralstat in 20% TPGS	Yes	8348815
*As part of the 28-day repeat dose toxicity study in rats						

Carcinogenicity

Carcinogenicity was assessed in rats and mice in GLP compliant studies of appropriate design. Pharmacological response and metabolic similarity in both species were demonstrated and studies dosed by the oral route which is intended for this indication.

Table 7: Summary of Carcinogenicity Studies Conducted

Type of Study	Species, Strain	Duration of Dosing	Route of Administration/ Dose ^a	Compound Administered	NOAEL mg/kg/day	GLP Compliance	Report/ Study Number
10-day and 28-day range finder toxicity study	Mouse, Wild Type CByB6F1/Tg(HRAS)2Jic	10 days and 28 days	10-day phase: oral 0, 100, <u>300</u> , 1,000, 1,500 mg/kg/day 28-day phase: Males: oral 0, <u>300</u> , 600, 1,000 mg/kg/day	Sebetralstat in 0.5% HPMC	300	Yes	20196412

			Females: oral 0, 300, 750, 1,500 mg/kg/day				
26-week carcinogenicity study	Mouse, CByB6F1/Tg (HRAS)2Jic	26 weeks	Males: oral 0, 20, 65 and 200 mg/kg/day Females: oral 0, 30, 100 and 300 mg/kg/day	Sebetralstat in 0.5% HPMC	200 (M) 300 (F)	Yes	20235986
13-week toxicity study	Rat, Crl:WI(Han)	13 weeks	Oral 0, 3, 10, 30 mg/kg/day	Sebetralstat in 0.5% HPMC	30	Yes	JAM0043
104-week carcinogenicity study	Rat, Crl:WI(Han)	104 weeks	Males: oral 0, 30, 100 and 300 mg/kg/day Females: oral 0, 30, 100 and 300 mg/kg/day	Sebetralstat in 0.5% HPMC	300 for malignant tumours 30 (M) and 100(F) for benign tumours	Yes	JAM0025

Carcinogenicity risk was evaluated in a 26-week transgenic mouse study and a 104-week rat study. In the mouse study (20235986), sebetralstat was not carcinogenic when administered up to 200 mg/kg/day in males and 300 mg/kg/day in females, the high doses selected for the study. Exposures at these NOAELs correspond to a 0.2-fold (as calculated by the Applicant based on comparison to clinically predicted AUC_{0-inf}) and 0.5-fold margin of safety in males compared to the MHRD for unbound plasma AUC and C_{max} , respectively and to a 0.4-fold (as calculated by the Applicant based on comparison to clinically predicted AUC_{0-inf}) and 1.0-fold margin for females based on unbound AUC and C_{max} , respectively. These exposure margins are low; however, high dose selection was based on prior studies indicating that higher doses would not be tolerated for chronic dosing.

In the 104-week rat study (JAM0025), no treatment-related increase in malignant tumours was noted. There was a treatment-related increased incidence of benign tumours in the liver (females), pituitary gland (males), thyroid (males), testes, and ovaries. The increased incidence of hepatocellular adenomas in female rats correlated with centrilobular hepatocellular hypertrophy, a common adaptive response to xenobiotics, which was observed in females at ≥ 100 mg/day and in both sexes in the 300 mg/kg/day dose groups. The increased incidence of benign adenomas in the pituitary in high dose males may correlate with increased incidence and/or severity of focal hypertrophy and vacuolation in pars distalis that was observed in all sebetralstat treated males. In the thyroid, a higher instance of follicular cell adenomas in high dose males was not statistically significant. This was accompanied by observations of pre-neoplastic changes of increased incidence of focal follicular cell hyperplasia in thyroids of high dose males and both mid and high dose females. While evidence of progression from hyperplasia to adenoma was seen in high dose males, this was not evident in females at either dose. It was considered that the neoplastic and pre-neoplastic changes of follicular cell origin could result from increased thyroid hormone excretion due to enzyme induction. In the testes, Leydig cell benign tumours were observed a statistically significantly increased incidence in mid and high dose males. In ovaries a low incidence of benign granulosa cell tumours was observed in all sebetralstat treated groups and a single instance of malignant granulosa cell tumour in one high dose female. The combined incidence of these neoplasms was increased, though not statistically significantly, at 300 mg/kg/day. There was also an observation of increased incidence and severity of interstitial cell hyperplasia in the ovaries of high dose females.

The histopathology evaluation concluded that cytology and architecture of tumours in treated groups were similar to those in control animals suggesting potential for augmentation of spontaneous tumours. Notable findings occurred in endocrine and reproductive organs. These observations, together with corresponding non-neoplastic findings in the liver, pituitary, ovaries, adrenals and thyroids, are overall suggestive of an adaptive response in the liver and mild hormonal perturbation, potentially disrupting normal homeostatic feedback mechanisms on the hypothalamic-pituitary-gonadal axis. The No Observed Effect Level (NOEL) for benign tumour formation in this study was 30 mg/kg/day for males, based on the increased incidence of benign tumours of Leydig cells of the testes in the 100 and 300 mg/kg/day dose groups. In general, the occurrence of Leydig cell tumours in rodents, particularly rats, are considered of little relevance to human health (Steinbach, Thomas J. et al. Human Relevance of Rodent Leydig Cell Tumors. (2015) <https://doi.org/10.1002/9781118834015.ch109>). The NOEL for females was 100 mg/kg/day, based on the increased incidence of benign liver tumours observed at 300 mg/kg/day. Clinical relevance of the occurrence of benign liver tumours is limited since these are considered resulting from the adaptive response noted in the livers of rats administered daily dose of sebetralstat in chronic studies. No such liver or endocrine organ associated changes were noted in the 13-week daily or intermittent dosing studies, or the pivotal 26-week intermittent dosing study in NHPs. The NOAEL for carcinogenicity was 300 mg/kg/day. Safety margins at the NOAEL to clinical exposure at the MRHD are 5.7-fold for unbound plasma AUC and 2.0-fold for unbound plasma C_{max} .

Reproductive and Developmental Toxicology

Reproductive and developmental toxicity has been examined in a GLP compliant battery of studies including fertility and early embryonic development, embryofetal development and pre- and postnatal development studies in rats and in embryofetal development studies in rabbits. Whilst the rat is a pharmacological responder with similar metabolism to man, and metabolism was similar in rabbits, sebetralstat did not inhibit rabbit PKa in an isolated enzyme inhibition study.

The reproductive and developmental toxicity studies conducted are summarised in the table below:

Table 8: Summary of Reproductive and Developmental Toxicity Studies

Type of Study	Species, Strain	Duration of Dosing	Route of Administration/ Dose	Compound Administered	NOAEL mg/kg/day	GLP	Report/ Study Number
Combined fertility and early embryonic development study	Rat, Crl:WI(Han)	14 days and until GD6	Oral 0, 100, 300, <u>600</u> mg/kg/day	Sebetralstat in 0.5% HPMC	600	Yes	JAM0012
Embryo-fetal development range finder study	Rat, Crl:WI(Han)	From GD6 to GD17	Oral 0, 100, 300, 1,000 mg/kg/day	Sebetralstat in 20% TPGS	300	Yes	JAM0005
Embryo-fetal development study	Rat, Crl:WI(Han)	From GD6 to GD17	Oral 0, 100, <u>300</u> , 600 mg/kg/day	Sebetralstat in 0.5% HPMC	Maternal and fetal 300	Yes	JAM0013
Non-pregnant 7-day tolerability study	Rabbit, New Zealand White	7 days	Oral 0, 100, 300, 500, 600 mg/kg/day	Sebetralstat in 20% TPGS	600	No	JAM0003
Non-pregnant formulation bridging study	Rabbit, New Zealand White	7 days	Oral 100, 300 mg/kg/day	Sebetralstat in 0.5% HPMC	NA	No	JAM0011

Embryo-fetal development range finder study	Rabbit, New Zealand White	From GD6 to GD18	Oral 0, 100, 300, 400 mg/kg/day	Sebetralstat in 20% TPGS	300	Yes	JAM0004
Embryo-fetal development study	Rabbit, New Zealand White	From GD6 to GD18	Oral 0, 30, 100, <u>300</u> mg/kg/day	Sebetralstat in 0.5% HPMC	Maternal 100 Fetal 300	Yes	JAM0014
Pivotal Pre- and Postnatal Development study	Rat, Crl:WI(Han)	From GD6 to Day 20 lactation	Oral 0, 100, 200 or <u>450</u> mg/kg/day	Sebetralstat in 0.5% HPMC	450	Yes	JAM0060

In a fertility and early embryonic development study (JAM0012), sebetralstat did not affect mating performance, sperm parameters or pregnancy parameters. For the high dose group (600 mg/kg/day), mean pregnancy parameters were not statistically different to concurrent controls and, except for % preimplantation loss, were within historical control range. The higher group mean incidence of pre-implantation loss in high dose females was observed (16.2% vs 8.6% in concurrent controls), was outside of the upper range of historical control data (13.4%). This was attributed to 2 females with only 1 or 2 implantations. In the female with the single implantation, this was an early intrauterine death and as a consequence the group mean % post-implantation loss was also slightly higher than concurrent controls. However, overall group mean for % post implantation loss was within the historical control range. The NOEL for male fertility, female fertility and early embryonic development was considered to be the high dose, despite these findings. This study indicates that there could be potential for sebetralstat to cause pre-implantation loss at 600 mg/kg/day in rats, and the NOAEL. However, it was accepted that the higher mean pre-implantation loss in the high dose group could be due to natural biological variability and not a sebetralstat-related effect. The NOAEL of 600 mg/kg/day is accepted.

Exposures at 600 mg/kg/day, the NOAEL for fertility, result in safety margins to clinical exposure at the MRHD of 7.7-fold and 2.6-fold for unbound plasma AUC and C_{max}, respectively.

Embryo-fetal development was evaluated in rats and rabbits. In two GLP compliant EFD studies in rats (JAM0005, JAM0013), sebetralstat administration during the period of organogenesis was associated with adverse outcomes at doses >300 mg/kg/day. Doses of 1000 mg/kg/day in the DRF study (JAM0005) resulted in maternal toxicity consisting of initial body weight reduction resulting in lower body weight gain and decreased mean fetal weight. Pregnancy parameters were unaffected; however, there were instances of major fetal abnormalities (5 fetuses from 3 litters). In the pivotal study (JAM0013), doses of 600 mg/kg/day resulted in maternal toxicity consisting of lower body weight gain, resulting in lower fetal weight, an increased incidence of post-implantation loss and reduced mean number of liver fetuses per litter. In addition, developmental toxicity was observed, with increased incidence of minor abnormalities and of major abnormalities which were observed in 11 fetuses from 5 litters. In both these studies, no adverse effects were noted at the mid dose of 300 mg/kg/day, which was considered the NOAEL. Exposure margins at the NOAEL are 3.0-fold and 0.8-fold greater than clinical exposures at the MHRD based on unbound plasma AUC and C_{max}, respectively.

In two GLP compliant EFD studies in rabbits (JAM0004; JAM0014), sebetralstat was administered at doses up to 400 mg/kg/day during the period of organogenesis. Doses of 400 mg/kg/day in the DRF study (JAM0004) resulted in maternal toxicity consisting of body weight loss, reduction in food consumption, which resulted in lower fetal weight. Pregnancy parameters were unaffected and this study determined the acceptable top dose for the pivotal

study of 300 mg/kg/day. In the pivotal study (JAM0014), doses of 300 mg/kg/day were associated with body weight loss during the early dosing period resulting in a lower body weight gain compared with controls during the dosing period. Mean food consumption was also lower during the dosing period for this group but food intake and body weight gain on cessation of dosing was similar to controls. There was a slight reduction in mean fetal weight in this group. The Applicant concludes that incidence, nature or distribution of major malformations was not affected by sebetralstat administration. At 300 mg/kg/day a slightly higher incidence of minor fetal skeletal abnormalities was noted and given the slightly lower fetal weights in this group was attributed to a developmental delay considered reversible on cessation of dosing.

The pivotal rabbit study results are difficult to interpret due to an incidence of malformations occurring in all sebetralstat treated dose groups without apparent dose response, and that malformations noted in this study were within historical background control ranges for this species/strain in the testing laboratory in terms of nature, incidence and intergroup distribution of the major abnormalities. Exposure margins at the highest dose level of 300 mg/kg/day are 6.8-fold and 3.9-fold greater than clinical exposures at the MHRD based on unbound plasma AUC and C_{max} , respectively.

Furthermore, it is also noted that sebetralstat did not inhibit recombinant rabbit PKa (IC_{50} was $>40,000$ nM and $>6,623$ -fold the human K_i) in an *in vitro* study (058_KV123900_PH_2016) and therefore the rabbit does not appear to be a pharmacologically relevant species for evaluation of on-target effects of sebetralstat on embryofetal development. The findings in the rabbit studies may therefore be of limited relevance to assess risk to humans. On the basis of further information provided, it was agreed that the rabbit is an acceptable model for evaluation of off-target effects of sebetralstat and that selection is consistent with recommendations. It is noted that maternal toxicity was observed at the high dose in this study which would also not be expected to be an on-target effect indicating sufficiently high doses were administered in this study.

In a pre- and post-natal development study in rats (JAM0060), while there were some minor differences compared to controls were noted in some parameters (gestation length in P generation, pup body weight gain, time to completion of eyelid separation of pups, motor activity in F1, early deaths and post implantation loss in F1), these differences were small, and/or lacked a dose-response and overall none were considered adverse. TK evaluation was not conducted in this study, having been evaluated previously in pregnant rats in the EFD study. At the NOAEL of 450 mg/kg (high dose), exposures are expected to be higher than those observed at 300 mg/kg/day in the pivotal EFD study. This would result in safety margins of >3 and >0.8 fold at the MRHD for unbound plasma AUC and C_{max} , respectively.

A pivotal juvenile animal study has not been conducted, this is acceptable given the targeted patient population.

Other studies

Two impurities were identified for qualification in line with ICH Q3A and ICH M7 guidance. Both were evaluated in GLP-compliant *in vitro* bacterial reverse mutation (Ames) (JAM0094, JAM0098) and micronucleus assays (JAM0095, JAM0099). No mutagenic, clastogenic, or aneugenic effects were observed under the tested conditions, with all responses falling within historical control ranges.

Sebetralstat was not considered to be phototoxic when evaluated in a battery of studies consistent with guidelines, including a GLP-compliant study in 3T3 fibroblasts (20276285).

Exposure Safety Margins

The exposure margins from pivotal toxicology studies to a maximum human dose treatment of 900 mg are presented in Table 8. The exposure margins shown are from the longest term (26-week) toxicology studies, pivotal reproduction toxicology studies, the 26-week mouse and 104-week rat carcinogenicity studies, and single dose safety pharmacology studies. All exposure margins are calculated using unbound plasma concentrations of sebetralstat.

Table 9: Unbound Plasma Exposure Safety Margins of Sebetralstat to a Maximum Human Clinical Dose of 900 mg

Key Studies	Dose (mg/kg)	AUC ^a (h•ng/mL)	C _{max} ^a (ng/mL)	AUC Margin	C _{max} Margin
Single Dose Safety Pharmacology Studies					
Rat CNS Irwin (6 males/dose) ^b					
8348817	1,000 (NOAEL)	28,002	1,412	4.3x	0.7x
Rat Respiratory (6 males/dose) ^b					
8348816	1,000 (NOAEL)	28,002	1,412	4.3x	0.7x
NHP Cardiovascular (4 males/dose)					
8362593	300 (NOAEL)	11,543	2,226	1.8x	1.1x
Longest Term Repeat Dose Toxicity Studies					
26-week toxicity study in rat (15/sex/dose)					
8418576	300 (NOAEL)	38,337	3,760	5.8x	1.9x
26-week twice weekly dosing toxicity study in NHP (4/6/sex/dose)					
20286942	300 (NOAEL)	15,942	3,651	2.4x	1.8x
Pivotal Reproduction Toxicity Studies					
EFD toxicity study in rat (20 females/dose)					
JAM0013	300 (NOAEL)	19,890	1,685	3.0x	0.8x
	600 (LOAEL)	79,950	5,733	12x	2.9x
EFD toxicity study in rabbit (22 females/dose)					
JAM0014	300 (NOAEL)	44,875	7,788	6.8x	3.9x
Fertility and early embryonic development toxicity study in rat (20/sex/dose)					
JAM0012	600 (NOEL)	50,310	5,109	7.7x	2.6x
PPND toxicity study in rat (22 females/dose)					
JAM0060 ^c	450 (NOAEL)	19,890	1,685	3.0x	0.8x
Carcinogenicity Studies					
26-week carcinogenicity study in transgenic mouse (25/sex/dose)					
20196412	Male: 200 (NOAEL)	1,505	1,003	0.2x	0.5x
	Female: 300 (NOAEL)	2,879	1,900	0.4x	1.0x
104-week carcinogenicity study in rat (50/sex/dose)					
JAM0025	300 (NOAEL)	37,323	3,900	5.7x	2.0x

Estimated human unbound AUC and C_{max} of 6,566 h•ng/mL and 1,991 ng/mL respectively

NOAEL: No Observed Adverse Effect Level

LOAEL: Lowest Observed Adverse Effect Level (defined as the dose immediately above the NOAEL dose)

NOEL: No Observed Effect Level

^a In repeat dose studies, AUC and C_{max} values are based on mean plasma concentrations at the end of the study

^b Plasma sampling was not performed in these studies. Exposure margins are calculated to Day 1 exposure in male rats at 1,000 mg/kg in Study 8348815 (same dose level, dose vehicle and sex)

^o Plasma sampling was not performed in the PPND study JAM0060. The NOAEL in this study was the highest dose level (450 mg/kg); exposure margins to a lower dose of 300 mg/kg in the same dose vehicle in Study JAM0013 (pregnant females) are presented in the table

Conclusion

Toxicity of sebetralstat has been evaluated in a non-clinical program consistent with relevant guidance. The primary target organ of toxicity following daily administration in mice, rats and NHPs was identified as the liver, with similar findings across species which were largely reversible when dosing ceased. In intermittent dosing studies in NHPs (twice weekly dosing), no adverse liver findings were noted. Sebetralstat was not genotoxic, nor was it carcinogenic in mice. In rats, there was an increase in benign tumours in the liver, pituitary, thyroid, testes and ovaries, considered to be an exacerbation of spontaneous tumours secondary to adaptive responses to sebetralstat administration and mild hormonal perturbation. Sebetralstat did not affect fertility, embryofetal development or pre-or post-natal development at clinically relevant exposures in rats. However, sebetralstat was clearly associated with malformations at high doses in excess of clinically relevant exposures in rats. The EFD study in rabbits also resulted in malformations, though results were difficult to interpret. Given that sebetralstat was shown not to inhibit rabbit PKa, pharmacological relevance for on-target effects in this species is doubtful.

Overall, the toxicological studies support the use of sebetralstat for the targeted indication.

III.5 Ecotoxicity/Environmental Risk Assessment

A full Environmental Risk Assessment (ERA) was submitted with this application

A Phase II Tier A ERA was prepared in support of the Marketing Authorisation Application seeking approval of sebetralstat for the treatment of attacks of HAE. Following patient use and excretion, sebetralstat residues are expected to enter the aquatic environment via effluent discharges from STPs. The $PEC_{SURFACEWATER}$ is 0.0171 µg/L. Sebetralstat is not readily biodegradable and does not adsorb to sludges in a STP, it has a tendency to adsorb to some soils, but this is unrelated to the organic carbon content. The results from an aerobic transformation in aquatic sediment systems study indicated that [¹⁴C]-Sebetralstat dissipates from aerobic aquatic systems mainly via binding to sediment (NER), and the formation of transformation products (pyrazole-desmethy-sebetralstat). Mineralisation to carbon dioxide is not a significant route of degradation. Overall DT₅₀ values indicate that sebetralstat and its major transformation product may be considered very persistent in certain aquatic sediment systems. Based on >10% sebetralstat partitioned to sediment, a sediment toxicity study (OECD Guideline 218) was triggered.

Sebetralstat concentrations in surface water, groundwater, microorganisms, and sediment were estimated by applying conservative assumptions with respect to the compound's biodistribution and partitioning characteristics. The PNECs were estimated for surface water, groundwater, microorganisms in an STP and sediment, based on ecotoxicological testing data for three aquatic trophic levels, wastewater microorganisms and a sediment dwelling species. The requirements for a Phase II Tier (a risk assessment according to the current EMA 2006 Guideline), is to demonstrate acceptable risk to the surface water, groundwater, microorganisms in STPs, sediment and a review of the n-octanol-water partition coefficient. Based on the Phase II Tier A assessment presented, the potential risk to surface water, groundwater, wastewater microorganisms, and sediment is minimal.

Although there could be a potential risk for sebetralstat to accumulate and persist in some aquatic sediment systems, this risk is considered minimal. The standard wording is proposed for the SmPC and Patient Information Leaflet for use and disposal of unused drug.

Comment

A Phase II Tier A assessment has been presented consisting of a series of studies determining the environmental fate and effects of sebetralstat, an environmental exposure assessment and calculation of risk characterisation ratios, consistent with appropriate guidelines. The Phase II assessment report has been compiled by a suitably qualified expert,. Studies were conducted according to OECD methods and in compliance with GLP.

Sebetralstat was not readily biodegradable when assessed in accordance with OECD test method 301b. When tested in adsorption studies in accordance with OECD 106, sebetralstat did not adsorb to sludges in STP, but had a tendency to adsorb to some soils, though this was not proportional to the organic carbon content. The Applicant proposes that it is more likely the adsorption is dependent on pH and clay content. The results from an aerobic transformation in aquatic sediment systems study (OECD 308) indicated that sebetralstat dissipates from aerobic aquatic systems mainly via binding to sediment non-extractible residues, and the formation of transformation products (pyrazole-desmethyly-sebetralstat), with mineralisation to carbon dioxide an insignificant route of degradation. Overall, this study indicated that sebetralstat and its major transformation product may be considered very persistent in certain aquatic sediment systems and based on >10% sebetralstat partitioned to sediment, a sediment toxicity study (OECD 218) was triggered.

Environmental effects of sebetralstat were investigated in sewage microorganisms (OECD 209), algae (OECD 201), daphnia (OECD 211) and fish (OECD 210) as well as the triggered OECD 218 study conducted in sediment dwelling midges. Appropriate points of departure from these studies were utilised to calculate predicted no-effect concentrations. PNECs were then compared to the predicted environmental concentrations and risk quotients calculated. All risk quotients were found to be below trigger values for further evaluation.

The presented ERA is acceptable and no further evaluation is required and an appropriate statement is included in the product information.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

For this marketing application, the clinical development program for sebetralstat has included:

- Ten Phase 1 trials conducted in healthy subjects, but also including some cohorts of patients with hepatic impairment
- One Phase 2 double-blind, randomized, crossover, placebo-controlled efficacy and safety trial in adult patients with HAE Type I or II (KVD900-201)
- One pivotal Phase 3, double-blind, randomized, crossover, placebo-controlled efficacy trial in adult and pediatric patients aged 12 years and older with HAE Type I or II (KVD900-301)
- One ongoing Phase 3 open-label safety trial of long-term use of sebetralstat in adult and pediatric patients aged 12 years and older with HAE Type I or II that also provides supportive efficacy information (KVD900-302)
 - o This marketing application has been submitted with interim data from the open-label Phase 3 trial while the trial is still ongoing (data cutoff date of 31 January 2024; data fully cleaned to 15 December 2023).

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

In support of the application, the following were submitted (table 9):

Table 9. Description of clinical pharmacology trials

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
Healthy Subjects PK and Initial Tolerability Trials					
KVD900-101/ Completed	Phase 1, randomized, double-blind, placebo controlled, three-part, single ascending dose trial with formulation crossover, and food effect	Safety and tolerability of single ascending doses of sebetralstat Comparative bioavailability of different formulations of sebetralstat Food effect on the bioavailability of sebetralstat	N=84 84 males, 0 females 35.1 $\pm$ 9.9 years (19 - 55) Black or African American/white/other: 0/83/1	Healthy males between the ages of 18 and 55	Part A: Single ascending doses of sebetralstat 5 to 600 mg capsule (powder in capsule formulation) Part B: Single administrations of sebetralstat 100 mg capsule (powder in capsule formulation) or uncoated tablet Part C: Single administrations of sebetralstat 600 mg (6 $\times$ 100 mg) film-coated tablet under fed and fasted conditions Matching placebo
KVD900-102/ Completed	Phase 1, randomized, double-blind, placebo-controlled, multiple-administration, multiple-cohort	Safety and tolerability of multiple administrations of sebetralstat Effects of sebetralstat on ECG parameters	N=42 25 males, 17 females 40.4 $\pm$ 10.6 years (19 - 55) Black or African American/white/other: 21/16/5	Healthy males and females between the ages of 18 and 55	Multiple administrations: Three administrations of sebetralstat 600 mg (6 $\times$ 100 mg film-coated tablets) given at q2h, q4h, or q8h intervals Matching placebo
KVD900-103/ Completed	Phase 1, open-label absorption, metabolism, and excretion	Safety and tolerability of single administration of sebetralstat Mass balance of total radioactivity Routes and rates of elimination of sebetralstat and total radioactivity Metabolite profile of sebetralstat	N=6 6 males, 0 females 35.5 $\pm$ 11.7 years (23 - 54) Black or African American/white/other: 1/5/0	Healthy males between the ages of 18 and 55	Single administration (¹⁴ C)sebetralstat 600 mg (2 $\times$ 300 mg) powder in capsules
Comparative Bioavailability Trials					

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
KVD900-107/ Completed	Phase 1, open-label, randomized, single-administration, two-way crossover comparative bioequivalence	PK of a single administration of sebetralstat following administration of tablets that were either chewed or swallowed intact Safety and tolerability of a single administration of sebetralstat following administration of tablets that were either chewed or swallowed intact	N=26 16 males, 10 females 40.7 $\pm$ 9.84 years (19 - 54) Black or African American/white/white and black or African American: 3/22/1	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets that were either chewed or swallowed intact <u>Treatment A:</u> Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) tablets that were chewed at Hour 0 on Day 1 <u>Treatment B:</u> Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) tablets that were swallowed intact at Hour 0 on Day 1
KVD900-108/ Completed	Phase 1, open-label, randomized, single-administration, three-way crossover comparative bioavailability	PK of a single administration of sebetralstat following administration of ODTs or film-coated tablets Safety and tolerability of a single administration of sebetralstat following administration of ODTs or film-coated tablets under fasting conditions	N=36 11 males, 25 females 36.1 $\pm$ 9.92 years (20 - 54) Black or African American/white/white and black or African American: 4/30/2	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets, 500 mg (2 $\times$ 250 mg) ODTs, and 600 mg (2 $\times$ 300 mg) ODTs: <u>Treatment A:</u> Sebetralstat 600 mg (2 $\times$ 300 mg) ODTs at Hour 0 on Day 1 <u>Treatment B:</u> Sebetralstat 500 mg (2 $\times$ 250 mg) ODTs at Hour 0 on Day 1 <u>Treatment C:</u> Sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets at Hour 0 on Day 1
Drug-drug Interaction Trials					
KVD900-106/ Completed	Phase 1, four-part, multiple-period, open-label, fixed-sequence, two-period, DDI	Effects of multiple- administration itraconazole (Part 1), eltrombopag (Part 2), phenytoin (Part 3), and quinidine (Part 4) on the single-administration PK of sebetralstat	<u>Part 1:</u> N=17 16 males, 1 female 37.4 $\pm$ 9.20 years (21 - 52)	Healthy males and females between the ages of 19 and 55	Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets in the presence of index perpetrators: <u>Part 1:</u> Sebetralstat 600 mg alone (Day 1 of Period 1); itraconazole 200 mg

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
		Safety and tolerability of a single administration of sebetralstat alone and in combination with itraconazole (Part 1), eltrombopag (Part 2), phenytoin (Part 3), or quinidine (Part 4)	Black or African American/white/other: 10/7/0 Part 2: N=16 14 males, 2 females 38.4 $\pm$ 10.33 years (21 - 52) Black or African American/white/other: 7/9/0 Part 3: N=16 12 males, 4 females 40.9 $\pm$ 8.87 years (29 - 55) Black or African American/white/Asian: 7/8/1 Part 4: N=16 14 males, 2 females 38.5 $\pm$ 9.73 years (24 - 55) Black or African American/white/other: 6/10/0		(20 mL of 10 mg/mL) oral solution once daily for 6 days (Day 1 to Day 6 of Period 2); sebetralstat 600 mg co-administered with itraconazole on Day 5 Part 2: Sebetralstat 600 mg alone (Day 1 of Period 1); eltrombopag 75 mg (1 $\times$ 75 mg) tablet once daily for 8 days (Day 1 to Day 8 of period 2); sebetralstat 600 mg co-administered with eltrombopag on Day 7 Part 3: Sebetralstat 600 mg alone (Day 1 of Period 1); phenytoin 100 mg (1 $\times$ 100 mg) capsule three times daily for 15 days (Day 1 to Day 15 of Period 2); sebetralstat 600 mg co-administered with phenytoin on Day 14 Part 4: Sebetralstat 600 mg alone (Day 1 of Period 1); quinidine 600 mg divided into two administrations (1 $\times$ 300 mg tablet each) 1 hour prior to and 3 hours after a single administration of sebetralstat 600 mg on Day 1 of Period 2

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
KVD900-112/ Completed	Phase 1, 4-part, open-label, fixed-sequence, 2-period DDI	Effects of multiple administrations of verapamil (Part 1), multiple administrations of efavirenz (Part 2), single administration of cimetidine (Part 3), and multiple administrations of modafinil (Part 4) on the PK of a single administration of sebetralstat Safety and tolerability of a single administration of sebetralstat alone and in combination with verapamil (Part 1), efavirenz (Part 2), cimetidine (Part 3), or modafinil (Part 4)	Part 1: N=16 13 males, 3 females 40.9 $\pm$ 9.02 years (23 - 54) Black or African American/white/other: 2/13/1 Part 2: N=16 14 males, 2 females 40.9 $\pm$ 8.94 years (24 - 53) Black or African American/white/other: 2/14/0 Part 3: N=16 9 males, 7 females 41.3 $\pm$ 10.54 years (23 - 55) Black or African American/white/other: 1/14/1 Part 4: N=16 13 males, 3 females 45.8 $\pm$ 8.21 years (28 - 54) Black or African American/white/other: 2/13/1	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets in the presence of index perpetrators Part 1: Sebetralstat 600 mg alone (Day 1 of Period 1); verapamil 240 mg (1 $\times$ 240 mg) tablet for 6 days with sebetralstat 600 mg co-administered on Day 5 Part 2: Sebetralstat 600 mg alone (Day 1 of Period 1); efavirenz 600 mg (1 $\times$ 600 mg) tablet for 14 days with sebetralstat 600 mg co-administered on Day 14 Part 3: Sebetralstat 600 mg (Day 1 of Period 1); single administration of cimetidine 800 mg (4 $\times$ 200 mg tablets), with sebetralstat 600 mg co-administered on Day 1 of Period 2 Part 4: Sebetralstat 600 mg alone (Day 1 of Period 1); modafinil 200 mg (1 $\times$ 200 mg) tablet for 15 days with sebetralstat 600 mg co-administered on Day 14

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
Intrinsic Factor PK Trials					
KVD900-104/ Completed	Phase 1, open-label, single-administration, multiple group	Impact of hepatic impairment on the plasma PK profile of a single administration of sebetralstat Safety and tolerability of a single administration of sebetralstat in subjects with hepatic impairment and subjects with normal hepatic function Impact of hepatic impairment on secondary PK parameters of a single administration of sebetralstat	N=24 17 males, 7 females 59 $\pm$ 5.7 years (47 - 68) Black or African American/white/Asian: 3/20/1	Male and female subjects between the ages of 18 and 75 years with varying levels of hepatic function (mild hepatic impairment, moderate hepatic impairment, and matched controls)	Single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets
KVD900-110/ Completed	Phase 1, randomized, double-blind, placebo-controlled, single-administration ethnobridging trial	Safety, tolerability, and PK of a single administration of sebetralstat in Japanese, Chinese, and White subjects Assessment of the PKa enzyme activity as a PD biomarker	N=74 47 males, 27 females 39.3 $\pm$ 9.29 years (21 - 55) Japanese/Chinese/ White: 25/24/25	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 300 mg, 600 mg (2 $\times$ 300 mg), or 1,200 mg (4 $\times$ 300 mg) film-coated tablets Matching placebo

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
KVD900-109/ Completed	Phase 1, 2-part, trial Part 1: open-label Part 2: randomized, partially double-blind, placebo- and positive-controlled, 3-way crossover TQT	<u>Part 1:</u> to determine that the proposed suprathreshold dose regimen of sebetralstat is safe and tolerable and achieves the targeted suprathreshold peak plasma concentration <u>Part 2:</u> effect of suprathreshold dose regimen of sebetralstat on QTcF	<u>Part 1:</u> N=8 5 males, 3 females 35.9 $\pm$ 13.82 years (20 - 54) <u>Part 2:</u> N=30 24 males, 6 females 32.6 $\pm$ 10.13 years (19 - 55) White/black or African American/Asian/Native Hawaiian or other Pacific Islander: 23/5/1/1	Healthy males and females between the ages of 18 and 55	<u>Part 1:</u> Sebetralstat 900 mg (3 $\times$ 300 mg) film-coated tablets, every hour for 3 administrations (hours 0, 1, and 2) to total 2,700 mg <u>Part 2:</u> 3 treatments across 3 trial periods (1 treatment per period): • Treatment A: Sebetralstat 900 mg or 1,200 mg (3 $\times$ 300 mg or 4 $\times$ 300 mg, respectively) film-coated tablets; 900 mg (3 $\times$ 300 mg) given at 0 and 1 hours and 1,200 mg (4 $\times$ 300 mg) given at 2 hours, to total 3,000 mg • Treatment B: placebo for sebetralstat Treatment C: moxifloxacin 400 mg oral tablet, open-label

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
Patient PK and PD Trials					
KVD900-201/ Completed	Phase 2, two-part, two-sequence, two-period crossover Part 1 ^a : open-label Part 2: randomized, double-blind, placebo-controlled	Efficacy of sebetrastat compared to placebo in halting the progression of a peripheral or abdominal attack of HAE Safety and tolerability of sebetrastat PK profile of sebetrastat when taken during the intercritical period between HAE attacks PD profile of sebetrastat in reducing the concentration of residual cleaved HK during the intercritical period between HAE attacks PD profile of sebetrastat in reducing activated plasma enzyme activity during the intercritical period between HAE attacks	Total enrolled: N=68 31 males, 37 females 38.3 $\pm$ 13.23 years (19 - 68) Black or African American/white/other: 0/68/0 PK Analysis Set: N=42	Male or females aged 18 years and older with HAE Type I or II	<u>Part 1:</u> Open-label sebetrastat 600 mg (6 $\times$ 100 mg) film-coated tablets <u>Part 2:</u> Sebetrastat 600 mg (6 $\times$ 100 mg) film-coated tablets Matching placebo
KVD900-302a/ Ongoing	PK subtrial of KVD900-302 ^b	PK profile of sebetrastat in pediatric patients 12 to <18 years of age	PK samples available for 2 pediatric patients (both female, age 16) as of the data cutoff date for the interim KVD900-302 CSR	Male and female pediatric patients aged 12 to <18 years with HAE Type I or II who are participating in KVD900-302	Sample collection only in KVD900-302a As part of the main KVD900-302 trial, patients receive a single administration of sebetrastat 600 mg (2 $\times$ 300 mg) tablets to treat each HAE attack. If needed (as determined by the patient), an additional administration may be administered for each attack at least 3 hours after the first administration.
Modeling					

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
Report 3244-0007/ Completed	Population PK model to provide predictions for the sebetralstat dose level that would be the most appropriate for pediatric patients (12 to <18 years of age) to achieve comparable exposure to the adult population	An initial population PK model to describe the PK and variability of sebetralstat in adults (healthy subjects and patients with HAE) and to predict the PK exposure and variability in a pediatric population (12 to <18 years of age)	Simulation population: 600 subjects (200 males, 400 females) 12 to <18 years with body weight ranging from 31.0 to 93.3 kg	Data from KVD900-101 (healthy adult subjects), KVD900-102 (healthy adult subjects), and KVD900-201 (adult patients with HAE Type I or II)	Sebetralstat dose levels of 5 to 600 mg were used in the modeling
Report KVD900-PPK1_PPK/ Completed	Population PK model to characterize the PK of sebetralstat	To assess the impact of selected intrinsic (sex, age, weight, race, etc.) and extrinsic (food status, formulation, etc) factors on the exposure of sebetralstat To generate exposure parameters for sebetralstat (e.g. C_{max} , predicted plasma concentrations at 15 and 30 minutes, and AUC)	Simulation population: 1,200 pediatric subjects 2 to 5 years and 6 to 11 years of age (600 males, 600 females), 600 pediatric subjects 12 to <18 years of age (200 males, 400 females) and adults ($\geq$ 18 years of age)	Data from KVD900-101 (healthy adult subjects), KVD900-102 (healthy adult subjects), KVD900-104 (healthy adult subjects), KVD900-106 (healthy adult subjects), KVD900-107 (healthy adult subjects), KVD900-108 (healthy adult subjects), KVD900-110 (healthy adult white, Japanese, and Chinese subjects), and KVD900-201 (adult patients with HAE Type I or II)	Sebetralstat dose levels of 5 mg to 1,200 mg were used in the modeling
Report KVD900-PPK1_PPK_SI M1/ Completed	Population PK model of various dosing scenarios based on the intended commercial posology	To generate C_{max} and AUC predictions for different dosing scenarios of 3 x 300 mg sebetralstat	Simulation population: 500 adults ($\geq$ 18 years of age) with demographics from 97 patients with HAE Type I or II from KVD900-301	The population PK model developed in KVD900-PPK1_PPK was used to perform the simulations	Doses of 3 x 300 mg sebetralstat given 0, 0.75, 3 or 8 hours apart were simulated

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age $\pm$ SD (Range) Race	Trial Population	Dose Regimen
Report 019387J/ Completed	PBPK model to predict the PK of sebetralstat in subjects with severe hepatic impairment	Development, validation, and verification of PBPK model to predict the PK of sebetralstat in subjects with severe hepatic impairment	Not applicable	Data from KVD900-101 and KVD900-103 (single oral administrations from 5 to 600 mg) and KVD900-106 (DDI trial with itraconazole and quinidine) in healthy subjects were used to develop and validate the hepatic impairment model. Data from KVD900-104 were used to verify the model	Modeled single administration
Report 01937101/ Completed	PBPK model to assess the potential impact of increased stomach pH on rate and extent of sebetralstat absorption	Use of a PBPK model to assess the impact of different stomach pH on the PK of sebetralstat	Not applicable	The PBPK model developed and reported in 019387J was used to perform sensitivity analysis of different stomach pH on the PK of sebetralstat	Modeled single administration

^a Clinical pharmacology evaluations in Part 1 only of KVD900-201

^b Patients in the PK subtrial KVD900-302a receive sebetralstat in the main KVD900-302 trial, the ongoing Phase 3 open-label extension trial to evaluate long-term safety of sebetralstat. Dose regimen in KVD900-302 is a single administration of sebetralstat 600 mg (2 $\times$ 300 mg) film-coated tablets. If needed (as determined by the patient), patients are permitted to take an additional administration of sebetralstat 600 mg separated by at least 3 hours following the first administration. No modifications for administration of IMP are made because of participation in the PK subtrial

Overview of Bioanalytical Methods

Fully validated bioanalytical methods were used for measuring levels of sebetralstat in plasma or dried blood samples from clinical studies. The methods, calibration ranges, storage stability and corresponding validation reports are shown below:

Table 10: Summary of Bioanalytical Methods in Human Plasma and Dried Blood

Species/Sample Matrix	Analyte	Calibration Range	Method utilized	Stability	Study Number
Human plasma	Sebetralstat	1-1,000 ng/mL	LC-MS/MS	366 days (-20/-80°C; YDS/073)	YDS/072
Human plasma	Sebetralstat	100-50,000 ng/mL	LC-MS/MS	153 days (-20°C; YDS/133)	YDS/090
Human dried blood	Sebetralstat	40-20,000 ng/mL	LC-MS/MS	202 days (room temperature; YDS/118)	YDS/103

Bioanalysis was performed using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and all assays used D₈-deuterated sebetralstat (KV126341) as the internal standard. The specificity of the assay was evaluated as part of the validation process in the presence of concomitant medications used in drug-drug interaction (DDI) studies.

All samples were analysed within the validated frozen storage stability period. Incurred sample reanalysis was successfully demonstrated in all studies in which PK was determined.

Overview of Clinical Pharmacokinetics

In KVD900-101, concentrations of sebetralstat reached maximal plasma levels rapidly, with median T_{max} being 1 hour or lower in all fasted cohorts. The maximum observed plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) increased with increasing dose level in Part A. The terminal elimination half-life ($t_{1/2}$) of sebetralstat increased with increasing dose level as an additional, longer, elimination phase became evident. When fed (600 mg dosed in Part C), the median T_{max} was delayed and occurred at 2.5 hours. The delay to T_{max} in the fed state is consistent with delayed gastric emptying in the presence of food. No food effect was observed on overall exposure (AUC).

In KVD900-102, three administrations of 600mg sebetralstat were given 2, 4, or 8 hours apart. Following the first administration in each cohort, plasma sebetralstat concentrations increased rapidly to similar geometric mean maximum (C_{max} (Dose1)) of 3,920 ng/mL in Cohort 1 (q8h), 4,410 ng/mL in Cohort 2 (q4h), and 5,040 ng/mL in Cohorts 3 and 4 (q2h) and occurred at similar median T_{max} (Dose1) of 1.00 hours, 1.04 hours, and 0.88 hours, respectively. Following the third administration, geometric mean C_{max} (Dose3) increased compared with the first administration and the increase was more pronounced for Cohorts 3 and 4, which had the shortest dosing interval of 2 hours.

In KVD900-110, C_{max} and AUC were shown to be proportional between the 300 mg and 600 mg dose groups.

Following a single administration of [¹⁴C]sebetralstat 600 mg in KVD900-103, sebetralstat was characterized by rapid absorption in the systemic circulation, with a median T_{max} value of 0.5 hours in plasma. After reaching maximum observed concentration (C_{max}), plasma

concentrations of sebetralstat appeared to decline in a biphasic manner, with a mean $t_{1/2}$ of 6.68 hours. Fecal and urinary excretion accounted for a mean of 63.4% and 32.4% of the radioactive dose, respectively. Although sebetralstat was the largest drug-related component in feces and urine (mean of 12.5% and 8.66% of administered radioactivity respectively), there was extensive biotransformation to a variety of metabolites, indicating that clearance of sebetralstat was mainly via hepatic metabolism. No disproportionate or unique human metabolites have been observed, and the metabolic profile of sebetralstat is similar to that in the non-clinical toxicology species.

At supratherapeutic dose levels of 2,700 mg and 3,000 mg given over a 2-hour period in KVD900-109, neither C_{max} nor AUC increased between these two dose levels, and individual exposures spanned similar ranges.

As sebetralstat is indicated for the treatment of HAE attacks and will be taken by patients on an intermittent basis, patients will not be dosed to steady state. Exposure to sebetralstat will therefore effectively be limited to the day of treatment, and accumulation in the plasma is not expected.

The time to onset of efficacy is attributed to the PK profile of sebetralstat; sebetralstat is rapidly absorbed following oral administration, with plasma levels quickly reaching pharmacodynamically active levels.

Intrinsic Factors

The impact of patient population, age, race, and hepatic function were evaluated using data from dedicated clinical trials as well as population PK analyses. It was concluded that a dedicated renal impairment trial was not required; further detail is provided below.

Patient Population

Forty-two patients with HAE Type I or II were included in PK analyses in the Phase 2 trial KVD900-201. Prandial state was not controlled. There were no meaningful differences observed in the PK profile of patients with HAE from KVD900-201 compared with healthy subjects in Phase 1 trials (Module 2.7.2). Results were similar across all participants (healthy subjects and patients), trials, and cohorts.

Age

An initial population PK model based on data collected earlier in the development program was developed (Study 3244-0007). Simulations were undertaken to provide predictions of sebetralstat exposure in pediatrics (≥ 12 to < 18 years of age) to support their inclusion in the Phase 3 trials.

Sebetralstat exposure in the simulated pediatric population was considered similar to that in adults. A final population PK model was subsequently developed with additional Phase 1 trial data (KVD900-PPK1_PPK) and evaluated the impact of selected intrinsic factors, including age, on the exposure of sebetralstat. Simulated pediatric exposures were slightly increased compared with an adult exposure at the same dose level, but significant overlap existed at both simulated dose levels (300 and 600 mg).

KVD900-302a is an ongoing PK subtrial in pediatric patients aged ≥ 12 to < 18 years of age

being performed at a subset of sites participating in KVD900-302. The purpose of the PK subtrial is to confirm the PK modeling for pediatric patients. Patients receive up to 2 administrations of sebetralstat 600 mg for each attack as part of the main KVD900-302 trial.

As of the data cutoff date for this marketing application (31 January 2024), evaluable PK samples from 2 pediatric patients are available. Each patient's sebetralstat concentrations were plotted against the population-based model. Overall, based on the data available, the exposures observed in pediatrics were generally consistent with the model. The subtrial is ongoing; additional analysis will occur as more samples are collected from additional pediatric patients.

Race

KVD900-110 evaluated the PK and PD of three dose levels of sebetralstat in healthy adult White subjects compared with Chinese and Japanese subjects. The PK and PD of sebetralstat were comparable between subject groups.

No dose adjustments are needed based on race.

Hepatic Function

KVD900-104 was conducted to determine whether 600 mg sebetralstat PK parameters were altered in patients with impaired hepatic function to an extent that dose adjustments of sebetralstat in patients with hepatic impairment would be warranted. Study results indicated moderate hepatic impairment had an impact on the PK of sebetralstat (63% [1.6-fold], 100% [2.0-fold], and 100% [2.0-fold] increase of the geometric LS means of C_{max} , AUC_{0t} , and AUC_{inf} , respectively, compared with the normal hepatic function group). Geometric mean C_{max} , AUC_{0-t} , and AUC_{inf} of sebetralstat were comparable between subjects with mild hepatic impairment and normal hepatic function.

Given the proposed commercial dose of 300 mg, no dose adjustments are needed for patients with mild or moderate hepatic impairment, except in moderate hepatic impairment when taken with a strong CYP3A4 inhibitor, where a single dose of 300 mg is recommended. Use of sebetralstat in patients with severe hepatic impairment is not recommended.

Renal Function

In accordance with the US FDA Guidance: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing (2020) and EMA: Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014), an assessment of the impact of renal impairment on patients with HAE taking sebetralstat was performed. Renal excretion was not the primary route of elimination of sebetralstat. Unchanged drug in urine accounted for substantially less than 30% of the dose, with a mean of <9%, and no individual subject >13% (KVD900-103). Sebetralstat is primarily eliminated via metabolism in the liver to a range of different biotransformation products. It was concluded that a dedicated renal impairment trial was not required.

No dose adjustments are needed for patients with renal impairment.

Drug-drug Interactions

Sebetralstat is a substrate of cytochrome P450 (CYP) 3A4 and the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); the impact on sebetralstat clinical PK by inhibitors and/or inducers of these has been studied. Sebetralstat did not show any reversible- or time-dependent in vitro inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19 or CYP2D6. Direct (non-time dependent) inhibition of CYP2C9 and CYP3A4 was seen. In vitro induction of CYP3A4 at 10 μ M sebetralstat and above was observed. There was no or minimal induction of CYP1A2, 2B6, 2C8, 2C9, or 2C19. Sebetralstat in vitro did not inhibit P-gp and showed weak inhibition of BCRP. Sebetralstat caused in vitro inhibition of all studied renal and hepatic transporters other than OAT1.

No clinical DDI studies assessing the effect of sebetralstat on other medicinal products have been performed.

The Applicant acknowledges that for CYP and transporter inhibition, the unbound plasma C_{max} after a dose of 300 mg sebetralstat (or unbound $C_{max,inlet}$ in the case of OATP transporters) would result in values above the cut-off value for further investigation (ICH M12 Guideline, November 2024). Considering the intermittent administration of sebetralstat in the clinical setting, and the relatively rapid decrease of plasma levels after T_{max} , the Applicant believes that the risk of sebetralstat causing a clinically meaningful interaction with an object drug based on inhibition of CYP2C9, CYP3A4, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1, and MATE2-K is low. However, the Applicant has added wording to the 'Effects of Sebetralstat on other medicinal products' sub-section of part 4.5 of the Product Information to state that in vitro data suggests possible inhibition of CYP2C9, CYP3A4, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1, and MATE2-K, and that caution should be taken when dosing with narrow therapeutic index substrates of these enzymes and transporters, including taking these at different times of the day if possible. In addition, the Applicant has added wording to the 'Special warnings and precautions for use' part 4 of the Product Information to state that 'Sebetralstat is an in vitro inhibitor of MATE1, MATE2-K and OCT2 and co-administration may raise exposure to substrates of these transporters such as metformin. Clinicians should consider monitoring blood lactate and renal function inpatients who carry a higher risk for lactic acidosis.'

The impact of strong, moderate, and weak CYP3A4 inhibitors and inducers on the PK of sebetralstat was assessed in KVD900-106 and KVD900-112. In patients taking strong or moderate CYP3A4 inducers, it is recommended that an HAE attack is treated with a single administration of 900 mg (3 x 300 mg). In patients taking strong CYP inhibitors a single dose of 300 mg is recommended when treating and HAE attack. No dose adjustment is required with concomitant administration of weak CYP3A4 inducers or moderate or weak CYP3A4 inhibitors. Co-administration of P-gp and BCRP inhibitors had a relatively small effect on the PK of sebetralstat, and no dose adjustment is required when dosing with inhibitors of these transporters.

PBPK modelling of the predicted effect of gastric pH on the oral absorption of sebetralstat

The Applicant used PBPK modelling (using GastroPlus®) to predict the effect of acid raising agents (ARAs) on the oral absorption of sebetralstat. The Applicant provided qualification in the way of 39 literature examples where GastroPlus® has been used to predict the effect of drugs that modify gastric pH, including two that were accepted by the FDA. While there is

mis-prediction in some cases, which may preclude accurate quantitation of the effect, it is considered that the model is useful supporting information, particularly to support a minimal effect of drugs that modify gastric pH. The predictive performance of the sebetralstat model has also been demonstrated including the effect of food, formulation and co-administered agents.

It is suggested that the clinical risk of potential changes in the absorption and PK of sebetralstat caused by ARAs is considered to be low, this is supported by the PBPK model which predicts that F_a , C_{max} , and AUC_{0-inf} decreased from baseline by 10%, 30%, and 11%, respectively, on the 600 mg dose level under the fasting condition. The extent of the predicted changes was similar to the measured changes when 600 mg sebetralstat was given to fed subjects in KVD900-101, Part C (29% decrease in C_{max} ; no decrease in AUC). Also, analyses of data from the completed clinical trials, although based on low subject numbers, suggest that the response rates are similar between the groups with and without ARAs.

IV. 3 Pharmacodynamics

Pharmacodynamic data included in the dossier from KVD900-101 and KVD900-201 trials are summarised below.

PD activity of sebetralstat in plasma samples was evaluated using assays to determine inhibition of PKa enzyme activity and inhibition of DXS-activated PKa cleavage of HK to cHK.

KVD900-101 showed that mean inhibition of DXS-activated PKa activity in the plasma was increased with increasing plasma concentrations of sebetralstat and maintained above 95% for 3 to 4 hours at dose levels of sebetralstat 300 mg and 600 mg. Administration of 160 mg resulted in maximal mean inhibition of approximately 90% at 2 hours and less than 80% by 4 hours. As a result, a dose level of 160 mg did not provide sufficient PKa inhibition to fully suppress the contact system and was considered unlikely to demonstrate clinical efficacy.

Inhibition of PKa enzyme activity was shown to be similar between patients in KVD900-201 and the healthy subjects from KVD900-101.

No clinically significant food effect was observed on the PD profile of sebetralstat 600 mg provided in fed and fasted state in KVD900-101.

The inhibitory effect of sebetralstat on DXS-activated PKa enzyme activity as well as HK cleavage and consequent cHK formation were evaluated in patients from KVD900-201. The 600 mg dose level of sebetralstat achieved rapid and near complete inhibition of DXS-activated PKa activity in the HAE patient plasma samples. Onset of PKa inhibition was rapid, with 89% inhibition of PKa achieved at 15 minutes after dosing and maintained to the final PK/PD time point at 4 hours (94% inhibition). In addition, the 600 mg dose level of sebetralstat led to rapid inhibition of DXS-activated HK cleavage in the plasma samples. In pre-dose samples, DXS-activation induced near complete depletion of HK with corresponding increase in the appearance of cHK. DXS-activated post-dose plasma samples obtained at 15 minutes through 4 hours post-dose were all protected from DXS-activated depletion of HK and displayed cHK levels comparable with unstimulated plasma.

Although no formal comparison and analysis of results across trials have been conducted, there have been no meaningful differences observed in the PD profile between healthy subjects and patients with HAE (Figure 4). Results were similar across all participants (healthy subjects and patients), trials, and cohorts.

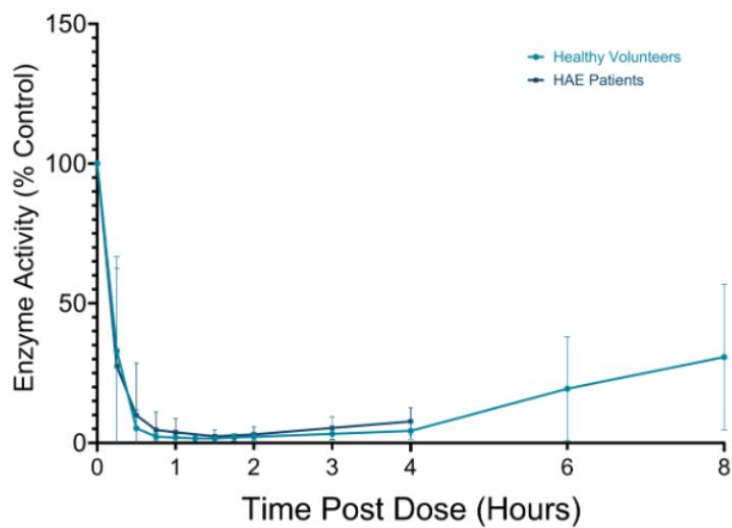


Figure 4: Enzyme Activity in Healthy Subjects and Patients with HAE after Sebetralstat 600 mg

Source: [200_KVD900_PH_2022 Appendix 1](#), [193_KVD900_PH_2021 Appendix 1](#)

IV.4 CLINICAL EFFICACY

Introduction

Primary evidence of clinical efficacy comes from the Phase 3 pivotal trial, KVD900-301, with supportive clinical efficacy from the KVD900-201 trial and the KVD900-302 trial as of a data cutoff date of 31 Jan 2024 (data fully cleaned to 15 Dec 2023). In support of the application, the following was submitted:

KVD900-301 (KONFIDENT trial)

Study 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 (KONFIDENT).

Methodology

KVD900-301 trial was conducted in patients 12 years or older with HAE Type I or II. Patients were randomly assigned to 6 treatment sequences in a 3-way crossover design. Eligible attacks were to be treated with a dose of placebo, 300 mg KVD900, or 600 mg KVD900 per attack with a minimum 48-hour washout period between each eligible attack and last dose of IMP or conventional on-demand treatment. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack.

The trial population included a subset of patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment. All patients were allowed to take conventional on-demand treatment. This trial was conducted at HAE treatment centers on an outpatient basis and comprised in-clinic and televisits. If an in-clinic visit could not be conducted (e.g., in the event of a pandemic or other reason that prevented the patient from attending the in clinic visit) home health visits (delegated home healthcare service provider) were to be performed, if permitted by the relevant regulatory authority, site's EC/IRB, local regulations, and the patient via informed consent.

Patients received the following treatments in a 1:1:1:1:1:1 ratio using a permuted-block randomization method, double-dummy blinded, crossover fashion to treat 3 separate eligible HAE attacks:

- 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 matching placebo tablet)
- 600 mg KVD900 (2 × 300 mg KVD900 tablets)
- Placebo for KVD900 (2 matching placebo tablets)

Efficacy and safety were assessed throughout the trial at in-clinic visits and televisits. Efficacy assessments included change in overall HAE attack symptoms assessed using the PGI-C, HAE attack severity assessed on the PGI-S, type of HAE attack symptoms, anxiety level assessed on the Modified GA-NRS, and time of conventional on-demand treatment use captured in the patient eDiary. Patients were to complete timed assessments of their HAE attack through 48 hours except during sleep; however, patients were asked to complete at

least the first 4 hours of diary assessments following the first administration of IMP. Safety assessments included AE assessments, physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory assessments.

Main inclusion criteria:

1. The trial population included male and female patients 12 years of age and older with a confirmed diagnosis of HAE Type I or II.
2. The trial population comprised 2 subsets:
 - a. patients who entered the trial taking only conventional on-demand treatment; and
 - b. patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.
 - i. 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.
3. Patient:
 - a. had at least 2 documented HAE attacks within 3 months prior to screening or randomization; or
 - b. was a completer of the KVD824-201 trial within 3 months prior to randomization and met all other entry criteria to enroll in KVD900-301.

Main 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. clinically significant history of poor response to BR2 blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the investigator

ObjectivesPrimary objective

To demonstrate the clinical efficacy of sebetralstat compared to placebo for the on-demand treatment of HAE attack.

Secondary objective

To investigate the safety and tolerability of Sebetralstat.

EndpointsPrimary endpoint

- 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.

Key secondary endpoints

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

Efficacy Assessment

Patient Global Impression of Change (PGI-C): 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse.

- *How would you describe your overall HAE attack symptoms right now, compared to how you were when you took the trial medication?*

Patient Global Impression of Severity (PGI-S): 5-point rating scale as *none, mild, moderate, severe, and very severe*.

- *What is your overall HAE attack severity right now?*

Sample size

A total sample size of approximately 114 patients were to be randomized to ensure approximately 84 patients completed the trial to ensure approximately 84 attacks were treated with placebo, 300 mg KVD900, and 600 mg KVD900. The trial population comprised 2 subsets: (1) patients who entered the trial taking only conventional on-demand treatment; and (2) patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

Efficacy Results

Primary endpoint

There was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg KVD900 (adjusted $p < 0.0001$) versus placebo group and between 600 mg KVD900 (adjusted $P = 0.0013$) versus placebo group.

The median (95% CI) time to the beginning of symptom relief was 1.61 hours (95% CI: 1.28, 2.27) for 300 mg KVD900 group, 1.79 hours (95% CI: 1.33, 2.27) for 600 mg KVD900 group, and 6.72 hours (95% CI: 2.33, not evaluable) for placebo group.

More attacks reached beginning of symptom relief within 12 hours of first IMP administration in the KVD900 treatment groups than placebo group (300 mg KVD900 group: 66 [75.9%] attacks and 600 mg KVD900 group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).

Key secondary endpoints

There was a statistically significant improvement in the time to reduction in severity between 300 mg KVD900 (adjusted $p = 0.0036$) versus placebo group and 600 mg KVD900 (adjusted $p = 0.0032$) versus placebo group. The median (95% CI) time to reduction in severity in PGI-S score was 9.27 hours (95% CI: 4.08, not evaluable) for 300 mg KVD900 group, 7.75 hours (95% CI: 3.27, not evaluable) for 600 mg KVD900 group, and not evaluable i.e., >12 hours for placebo group. More attacks achieved the time to reduction in severity in the 300 mg KVD900 (44 [50.6%] attacks) and 600 mg KVD900 groups (49 [52.7%] attacks) than placebo group (26 [31.0%] attacks).

There was a statistically significant improvement in the complete HAE attack resolution

between the 300 mg KVD900 group (adjusted $p=0.0022$) versus placebo group and 600 mg KVD900 group (adjusted $p<0.0001$) versus placebo group. The median (95% CI) time to complete HAE attack resolution was not evaluable (95% CI: 16.60, not evaluable) for 300 mg KVD900 group, 24.00 hours (95% CI: 10.6, not evaluable) for 600 mg KVD900 group, and not evaluable i.e., >24 hours for placebo group. More number of attacks reached complete HAE attack resolution within 24 hours of the first IMP administration in the 300 mg KVD900 (37 [42.5%] attacks) and 600 mg KVD900 groups (46 [49.5%] attacks) than placebo group (23 [27.4%] attacks).

The treatment effects for 300 mg KVD900 and 600 mg KVD900 groups were similar to the full FAS across all subgroups analyzed (including but not limited to baseline attack severity, initial attack location, use of long-term prophylactic treatment, and age of patient). For secondary and exploratory endpoints, time taken to achieve efficacy was consistent and supportive of the primary and key secondary endpoints.

KVD900-201

Study Title

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.

Methodology

This was a phase II, two-part, two-sequence, two-period (2x2) cross-over clinical study: Subjects with HAE type I or II were recruited through HAE treatment centers in Europe and USA.

In Part 1, subjects received 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 underwent a screening assessment for study inclusion, received study drug, followed by a 4 hour, in-clinic, safety, and PK/PD assessment.

In Part 2, the subjects were randomized 1:1 to 2 treatment sequences. This part of the study was conducted away from the clinic or hospital.

In Sequence 1 (study arm 1) subjects received a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects received a second single dose of placebo to treat the second eligible HAE attack.

In Sequence 2 (study arm 2) subjects received a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects received a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.

A minimum of 48-hour washout period was required between each dose of study drug. Laryngeal or facial attacks were not eligible for treatment. HAE attacks were treated within the first hour of onset and before reaching severe on the global attack severity scale.

Subjects were required to identify the start of a HAE attack. Upon onset of the eligible HAE attack, subjects notified the dedicated study physician or qualified designee with a description of the HAE attack. The dedicated study physician or qualified designee confirmed eligibility of the HAE attack and agreed to study drug being administered. HAE attacks required 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 took study drug, as instructed, and completed timed assessments of their HAE attack symptoms for a 48-hour period.

In the event that conventional attack treatment was used, the subject performed assessments every 30 min for 4 hours following first administration of conventional attack treatment. After this, the subject reverted back to original frequency of assessments based on time of study drug administration.

The dedicated study physician or qualified designee contacted the subject within 24 hours of the eligible HAE attack to confirm the subject's safety and wellbeing. Subjects were instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects contacted the dedicated study physician or qualified designee or contacted the nearest emergency service. The dedicated study physician or qualified designee was available 24 hours/day and 7 days/week to receive subject calls.

Subjects returned 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, blood sampling for laboratory safety measurements, and Subject Diary review.

Once two HAE attacks have been treated in Part 2, the subject returned to the clinic to undergo final safety checks including AE reporting, vital sign recording, blood sampling for laboratory safety measurements, and Subject Diary review.

Conventional attack treatment was permitted after 4 hours, or earlier as warranted, following study drug intake, provided HAE attack symptoms were judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or were deemed ineligible for study drug treatment, or were associated with laryngeal or facial symptoms. Prior to use of conventional attack treatment, subjects notified the dedicated study physician or qualified designee who confirmed conventional treatment was appropriate per protocol and subject report of symptom severity. Subjects were permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH intravenous [iv] or icatibant).

Key Inclusion criteria:

1. Male or female adult subjects 18 years of age and older.
2. Confirmed diagnosis of HAE type I or II at any time 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.

Key Exclusion criteria

Subjects were excluded from the study if one or more of the following statements were applicable at Screening (Visit 1) and on Visit 2:

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.

Objectives

Primary objective

To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of HAE.

Secondary objectives

- To investigate the safety and tolerability of KVD900.
- To investigate the 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 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.

Endpoints

Primary efficacy endpoint for Part 2 of the study:

- Time to use of conventional attack treatment within 12 hours of study drug.

Secondary efficacy endpoint for part 2 of the study:

- Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS):
 - o Worsening (including use of conventional attack treatment):
 - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 12 hours of study drug
 - Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 12 hours of study drug
- Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ):
 - o Improvement:
 - Time to symptom relief (“a little better” or higher for 2 consecutive time points) within 12 hours of study drug

- Visual Analogue Scale (VAS):
 - o Improvement:
 - Time to symptom relief (50% reduction from baseline in composite VAS for 3 consecutive time points) within 12 hours of study drug.

Efficacy Assessment

Patient Global Impression of Severity (PGI-S): Overall, HAE attack severity scored as none, mild, moderate, severe and very severe.

- *Please indicate the overall severity of your HAE attack right now.*

Patient Global Impression of Change (PGI-C): Change in HAE attack severity scored as Much better / Better / A little better / No change / A little worse / Worse / Much worse.

- *How would you describe your overall HAE attack symptoms right now, compared to how you were when you took the study drug?*

101-point visual analogue scale (VAS): The type of HAE attack symptoms (abdominal pain, skin pain and skin swelling) each assessed on a 100 mm visual analogue scale (VAS) anchored at 0 (none) and 100 (very severe).

- *How much abdominal pain / skin pain / skin swelling are you experiencing right now?*

Efficacy Results

Primary endpoint

The primary variable for statistical comparison between treatments in Part 2 of the study was the time to use of conventional attack treatment within 12 hours of study drug.

Following treatment with KVD900, use of conventional treatment was lower than compared with placebo. A higher proportion of subjects in the FAS did not use conventional attack treatment within 12 hours of study drug (84.9%) in comparison to following treatment with placebo (69.8%). Gehan's Generalized Wilcoxon Test showed a statistically significant difference in time to use of conventional attack treatment within 12 hours of study drug between KVD900 and placebo (p-value=0.0010). Gehan's Generalized Wilcoxon Test also showed a statistically significant difference in time to use of conventional attack treatment within 24 hours of study drug between KVD900 and placebo (p-value=0.0005).

Secondary endpoints

Efficacy Analysis PCI-S:

Following treatment with KVD900, PGI-S was improved compared to following treatment with placebo.

Following treatment with KVD900, a higher proportion of subjects in the FAS had improvement by one level or more from baseline in PGI-S within 12 and 24 hours of study drug in comparison to following treatment with placebo (56.6% and 30.2% within 12 hours and 66.0% and 37.7% within 24 hours, respectively). Gehan's Generalized Wilcoxon Test

showed a statistically significant difference in the time to improvement between KVD900 and placebo within both 12 (p-value=0.0002) and 24 hours (p-value=0.0008).

Following treatment with KVD900, a higher proportion of subjects in the FAS had complete HAE attack resolution defined as a severity rating of none on the PGI-S within 12 and 24 hours of study drug in comparison to following treatment with placebo (37.7% and 18.9% within 12 hours and 52.8% and 26.4% within 24 hours, respectively). Gehan's Generalized Wilcoxon Test showed a statistically significant improvement in time to HAE attack resolution between KVD900 and placebo within both 12 (p-value=0.0064) and 24 hours (p-value=0.0021).

Efficacy Analysis PCI-C:

Following treatment with KVD900, PGI-C was improved compared to following treatment with placebo. Following treatment with KVD900, a higher proportion of subjects in the FAS had HAE attack rated “a little better” or higher on PGI-C for 2 consecutive time points within 12 hours of study drug in comparison to following treatment with placebo. Gehan's Generalized Wilcoxon Test showed that the time to HAE attack rated “a little better” or higher on the PGI-C for two consecutive time points within 12 hour of study drug was statistically significantly shorter following KVD900 than following placebo (p-value=<0.0001).

Following treatment with KVD900, a higher proportion of subjects in the FAS had HAE attacks that were rated “a little better” or higher on the PGI-C for 2 consecutive time points within 4 hours of study drug in comparison to following treatment with placebo. Gehan's Generalized Wilcoxon Test showed a statistically significant decrease in the time to HAE attacks being rated “a little better” or higher for 2 consecutive time points between KVD900 and placebo within 24 hours (p-value=<0.0001).

KVD900-302 (KONFIDENT-S)

Study Title

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

Methodology

KONFIDENT-S (KVD900-302) is an ongoing trial being conducted on an outpatient basis and includes in-clinic or home health visits and televisits. If in-clinic visits cannot be conducted (eg, pandemic or for other reasons that prevented the patient from attending the in-clinic visits) home health visits are done if permitted by the relevant regulatory authority, and current national recommendations, Ethics Committee (EC)/Institutional Review Board (IRB), local regulations, and the patient via informed consent.

Approximately 150 patients (including a minimum of 12 adolescents) in total are planned to be enrolled in HAE centers worldwide. These patients will include rollover patients (those randomized in the KVD900-301 trial) and non-rollover patients (other patients including those randomized in the KVD900-201 Phase 2 trial or KVD900 naïve). As of the data cut-off for this interim report, 118 patients have been enrolled in the ongoing trial.

The screening period includes an in-clinic screening assessment. Screening for rollover patients following participation in the KVD900-301 trial was the same as the Final Visit in the KVD900-301 trial if the Final Visit from that trial was within 30 days of enrollment in KVD900-302. If the Final Visit of KVD900-301 was >30 days prior to rollover, a separate Enrollment Visit was completed. After screening, patients enter a 24-month treatment duration. Trial-related procedures are only performed after the patients signs the informed consent form (ICF).

Patients record HAE attacks in the eDiary for every HAE attack during the trial. Patients also complete the angioedema-quality of life (AE-QoL) questionnaire in the eDiary every 28 days through the end of the trial. In-clinic visits and televisits are performed to confirm KVD900 compliance, review the patient diary (and retrain, if necessary), and to undergo an AE and concomitant medication review.

On-Demand Treatment of HAE Attacks: Patients took a single dose of 600 mg KVD900 (2 × 300 mg tablets) for each HAE attack and were permitted to take additional doses of 600 mg KVD900 at least 3 hours following the first dose if attack symptoms persisted without improvement. Treatment was limited to no more than 2 doses (i.e. 1200 mg total daily dose [TDD]) within 24 hours (separated by at least 3 hours). Conventional on-demand treatment was permitted following KVD900 intake, provided HAE attack symptoms were judged severe enough by the patient to require treatment as per the patient's usual treatment regimen. Attacks that were not treated with KVD900 could be treated with conventional on-demand treatment per the patient's usual treatment regimen.

Laryngeal attacks were also treated immediately with conventional on-demand treatment if laryngeal attack symptoms worsened after initial treatment with KVD900.

Short-Term Prophylactic Therapy: Patients using only conventional on-demand treatment during the trial were permitted to use KVD900 as a short-term prophylactic therapy prior to undergoing surgical, dental, or medical procedures. Patients in all countries except the US, patients using long-term prophylactic treatment are not eligible to take KVD900 as short-term prophylactic therapy. For US patients, those on long-term prophylactic therapy were allowed to use KVD900 for short-term prophylactic therapy. The decision to use Short-Term Prophylactic Therapy is made on a case-by-case basis, after consultation between the investigator and the patient and based on whether treatment was medically appropriate.

Patients were required to take 3 doses of KVD900 in a 24-hour period with each dose approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure.

KVD900 could not be used for short-term prophylaxis if the patient had an attack within the last 48 hours or had not completed their last eDiary assessment for that attack.

Short-term prophylactic therapy was to be stopped if an HAE attack occurred that was treated with IMP or conventional on-demand treatment. If the attack started within 24 hours of the start of the procedure, the patient was to treat the attack with conventional on-demand treatment. If the attack started >24 hours after the start of the procedure, KVD900 could be used.

Treatment period:

Month 1-3 Visits: All patients returned to the site every month (± 1 week) for routine safety assessments (symptom-directed physical examinations, vital signs, and clinical labs). Adverse events, IMP dosing compliance, and concomitant medications were also reviewed.

Month 4-21 Visits: In-clinic visits occurred quarterly, and televisits occurred in the months in which the in-clinic visits did not (i.e. monthly visits were either in-clinic visits or televisits).

- At quarterly in-clinic visits (Months 6, 9, 12, 15, 18, and 21), patients returned to the site (± 1 week) for routine safety assessments, as outlined in the Schedule of Events (SOE).

Key Inclusion criteria

Rollover patients are eligible for inclusion if they meet all of the following criteria:

1. Patients are eligible to rollover in this trial if they were randomized in the KVD900-301 trial.

Non-rollover patients are eligible for inclusion if they meet all of the following criteria:

1. Confirmed diagnosis of HAE Type I or II at any time in the medical history:
2. Patient had at least 2 documented HAE attacks within 3 months prior to the Enrolment 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 Enrolment Visit. Patients in the US who are using danazol for prophylactic treatment prior to enrolment, are required to be on a stable dose and regimen for at least 6 months prior to the Enrolment Visit.

All patients are eligible for inclusion if they met all the following criteria:

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

Key Exclusion criteria

Rollover patients are excluded from participating in this trial if they meet any of the following criteria:

1. Discontinued from the KVD900-301 trial for reasons of non-compliance, withdrawal of consent, or safety.
2. Presented any safety concerns that precluded participation in the open-label trial as determined by the investigator.

Non-rollover patients are excluded from participating in this trial if they met any of the following 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 BR2 blocker, C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the investigator.

Objectives

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

1. To assess the long-term efficacy of KVD900 in the treatment of attacks in adolescent and adult patients with HAE Type I or II.
2. To assess the safety and efficacy of KVD900 when used as short-term prophylaxis in adolescent and adult patients with HAE Type I or II.

Endpoints

Primary endpoints - safety

1. Frequencies and percentages of patients with AEs, AEs within 3 days of IMP administration, serious AEs, and AEs causing premature discontinuation.
2. Number and percentage of patients with normal or abnormal laboratory results at each scheduled visit.
3. Number and percentage of patients with normal or abnormal vital sign results at each scheduled visit.

Secondary endpoints

1. 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.
2. 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.
3. PGI-S: time to HAE attack resolution defined as “none” within 24 hours of initial dose of IMP administration.
4. AE-QoL (exploratory): AE-QoL changes over time.
5. Time to first incidence of conventional on-demand attack treatment use within 12 hours and 24 hours.

Efficacy assessment

Patient Global Impression of Change (PGI-C): 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse.

Patient Global Impression of Severity (PGI-S): 5-point rating scale as *none*, *mild*, *moderate*, *severe*, and *very severe*.

Sample size

Up to 150 patients (including a minimum of 12 adolescents) were planned to be enrolled in the trial. The sample size was based on clinical considerations since no inferential statistical analysis was planned in the trial.

Efficacy Results

The primary endpoint in KVD900-302 is a safety endpoint. Refer to the clinical safety section for further information.

Key Secondary endpoints:

KVD900 showed consistent efficacy with comparable results between both rollover and non-rollover patients as well as with repeated treatment (Attack 1 to Attack 18).

1. 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.

A total of 639 HAE attacks were analysed, with 475 (74.3%) attacks achieving the beginning of symptom relief within 12 hours. Overall, the median time to beginning of symptom relief was 1.8 hours (95% CI: 1.77, 1.96).

2. 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.

A total of 640 HAE attacks were analyzed, with 330 (51.6%) attacks achieving a reduction in severity within 12 hours. The median time to reduction in severity was 6.57 hours (95% CI: 5.02, 8.82).

3. PGI-S: HAE Attacks That Resolved (defined as “none” on PGI-S) Within 24 Hours of Initial Dose of IMP Administration

A total of 640 HAE attacks were analysed, with 378 (59.1%) attacks achieving complete HAE attack resolution within 24 hours. The median time to achieve complete HAE attack resolution was 21.02 hours (95% CI: 18.55, 21.50).

Summary of Clinical Efficacy

The pivotal study KVD900-301 (KONFIDENT trial) was a double-blind, randomised, placebo-controlled, multicentre clinical trial in patients 12 years or older with HAE Type I or II where patients were randomly assigned to 6 treatment sequences in a 3-way crossover design. In addition to the inclusion and exclusion criteria to enrol participants, an eligibility criterion for what constitutes an attack whilst enrolled on the trial was determined in the protocol. Participants were treated for three attacks before they were considered to have completed the trial. Participants were randomly treated for each attack with either Sebetralstat 300mg (the sought-after dose), Sebetralstat 600mg or placebo by random assignment into one of six sequences and therefore were exposed to all three treatment options at the end of the trial.

Study KVD900-201 was a phase II, randomised, two-part, two-sequence, two-period (2x2) cross-over clinical study to evaluate the efficacy, safety, and tolerability of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack in adult subjects with HAE type I or II. The eligibility criteria were slightly different to that of KCD900-201 in that only patients with mild to moderate attacks and no facial attacks were included in the study. This was a two-part study where part two assessed efficacy of Sebetralstat. The treatment dose for was 600mg.

Study KVD900-302 is an open-label, multi-centre extension trial to evaluate the long-term safety of 600 mg KVD900 in patients 12 years of age or older with HAE Type I or II. The study included patients rolled-over from the phase III KONFIDENT trial and non-rollover patients. Participants enrolled into a 24-month treatment period. The study is currently ongoing.

Pivotal KONFIDENT trial

The overall median time from onset of attack to first IMP administration was 41 minutes [range: 6.0 to 140] (35 minutes for 300 mg KVD900 group, 41 minutes for the 600 mg KVD900 group, and 51 minutes for the placebo group). In the Safety Set, the majority of attacks were treated with 1 dose of IMP; the rate was higher in the KVD900 treatment groups compared to placebo group (53 [61.6%] attacks with 300 mg KVD900, 56 [58.9%] attacks with 600 mg KVD900 and 37 [44.6%] attacks with placebo). Where a second dose was taken, the median time between the 2 IMP doses was 3.858 hours for 300 mg KVD900 group, 3.783 hours for 600 mg KVD900 group, and 3.500 hours for placebo group.

The primary and key secondary endpoints in this trial were and the results were statistically significant. The primary efficacy endpoint of the trial was the time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) on the PGI-C within 12 hours of the first IMP administration. There was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg KVD900 (adjusted $p < 0.0001$) versus placebo group and between 600 mg KVD900 (adjusted $p = 0.0013$) versus placebo group. Time to symptom relief favoured Sebetralstat 300mg (1.61 hours) and 600mg (1.79 hours) compared to placebo (6.72 hours). More attacks reached beginning of symptom relief with 12 hours of first IMP administration in the KVD900 treatment groups than placebo group (300 mg KVD900 group: 66 [75.9%] attacks and 600 mg KVD900 group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).

The key secondary 1 endpoint was time to first incidence of decrease from baseline on the PGI-S (2 time points in a row) within 12 hours of the first IMP administration, i.e., time to reduction in severity. The key secondary 2 endpoint was time to complete HAE attack resolution defined as “none” on the PGI-S within 24 hours of the first IMP administration.

There was a statistically significant improvement in the time to reduction in severity between 300 mg KVD900 (adjusted $p = 0.0036$) versus placebo group and 600 mg KVD900 (adjusted $p = 0.0032$) versus placebo group. Time to reduction in severity was reached faster for attacks treated with 300 mg KVD900 and 600 mg KVD900 treatment groups compared with placebo group, with median times of 9.27 hours, 7.75 hours, and not evaluable i.e., >12 hours, respectively.

For key secondary endpoint 2, there was a statistically significant improvement in the time to complete HAE attack resolution between 300 mg KVD900 group (adjusted $p=0.0022$) versus placebo group and 600 mg KVD900 group (adjusted $p<0.0001$) versus placebo group. Complete HAE attack resolution was reached faster for attacks treated with 300 mg KVD900 and 600 mg KVD900 treatment groups compared with placebo group, with median times of 24 hours for 600 mg KVD900 group and not evaluable i.e., >24 hours (for 300 mg KVD900 and placebo groups).

The subgroup analysis generally supported the primary and key secondary endpoints. However, two areas of uncertainty remain around the efficacy of seabetalstat to treat severe HAE and patients on stable/short term plasma kallikrein inhibitors with break out attacks. Even though efficacy favoured participants who took seabetalstat, the number of severe HAE attacks were limited to around 17% of attacks.

Combined analysis of efficacy of phase II KVD900-201 and phase III KVD900-301

Noting that the phase II KVD900-201 study used a seabetalstat dose of 600mg, the combined efficacy analysis for the time to beginning of symptom relief within 12 hours of initial IMP administration favoured seabetalstat 300mg and 600mg. The median (95% CI) time to beginning of symptom relief of 1.61 hours (1.28, 2.27) for attacks treated with 300 mg, 1.83 (1.50, 2.27) hours for attacks treated with 600 mg, and 8.30 hours (4.00, NE [i.e. >12]) for attacks treated with placebo.

For the combined analysis of secondary endpoints, the median (95% CI) time to reduction in severity was 9.27 hours (4.08, >12) for attacks treated with 300 mg, 9.14 hours (5.53, >12) for attacks treated with 600 mg, and >12 hours for attacks treated with placebo.

For the time to complete resolution, number and percentage of patients who experienced complete attack resolution was 37 (42.5%) for attacks treated with 300 mg, 77 (51.0%) for attacks treated with 600 mg, and 38 (27.3%) for attacks treated with placebo. For attacks that reached complete attack resolution, median (95% CI) time to complete attack resolution was NE (i.e. >24 hours) (16.60, >24) for attacks treated with 300 mg, 24.00 hours (15.06, >24) for attacks treated with 600 mg, and >24 hours for attacks treated with placebo.

KVD900-302

Overall, the median time from onset of attack to the first IMP administration was 9.0 minutes (Q1-Q3: 1.0 to 69.0 minutes). Most patients (97.6%) were compliant with treatment and took 1 or 2 doses within 24 hours to treat the HAE attack.

Efficacy endpoints for this trial included time to beginning of symptom relief within 12 hours, time to first incidence of decrease within 12 hours (i.e. time to complete reduction in severity), time to attack resolution within 24 hours of first IMP administration (i.e. time to first complete HAE attack resolution), incidence of HAE attacks requiring conventional on-demand treatment of IMP within 12 and 24 hours, and AE-QoL changes over time.

Overall, the primary and secondary efficacy endpoints of this trial were met. Results showed consistent efficacy in both rollover and non-rollover patients and throughout repeated treatment

(Attack 1 to Attack 18). The beginning of symptom relief within 12 hours was achieved for the majority of HAE attacks (74.3%) at a median time of 1.8 hours.

A reduction in attack severity within 12 hours was achieved in 51.6% of HAE attacks at a median time of 6.57 hours. Complete HAE attack resolution within 24 hours was achieved in 59.1% of attacks at a median time of 21.02 hours. The frequency of on-demand conventional treatment was low within 12 and 24 hours (5.6% and 8.4% of the attacks, respectively). These results are in keeping with the KONFIDENT trial.

Conclusions on clinical efficacy

The clinical efficacy of Sebetralstat has been demonstrated against placebo.

IV.5 CLINICAL SAFETY

The safety profile for sebetralstat has been characterized using data from 13 clinical trials, including 10 Phase 1 trials, one Phase 2 trial, and two Phase 3 trials.

In the pivotal Phase 3 efficacy trial (KVD900-301), patients treated each eligible attack with 300 mg or 600 mg sebetralstat or placebo (up to 2 administrations per attack). In the ongoing Phase 3 open-label safety trial (KVD900-302), patients treat each attack with 600 mg sebetralstat (up to 2 administrations in a 24-hour period). In KVD900-302, patients could use sebetralstat as a short-term prophylactic therapy initiated prior to undergoing surgical, dental, or medical procedures. If they used the IMP for short-term prophylaxis, patients were instructed to take 3 administrations of sebetralstat, with each administration approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure.

In Phase 1 trials, clinical safety of sebetralstat has been evaluated at doses of 5 mg to 1,200 mg (maximum of 3,000 mg given over a 2-hour period).

Across trials, TEAEs were monitored starting from the time of first IMP administration through final visit/early termination; SAEs were monitored in Phase 2-3 trials from the time of signing informed consent. Clinical laboratory assessments, vital signs, and 12-lead ECGs were captured pre-dose and at pre-specified times post-dose in each trial. In the Phase 3 trials, complete physical examinations were performed at screening or enrollment visits, with symptom-directed physical examinations performed at the end of the trial or as noted in the protocol.

In the integrated analyses, a TEAE was defined as an AE that occurred or worsened on or after the time of the first IMP administration. Safety data collected from the Phase 1 trials were summarized separately from the Phase 2 and 3 trials. Data were not pooled across all phases due to differences in subject populations, trial designs, and duration of follow-up.

For safety analyses, an “exposure” is defined as all sebetralstat (or matching placebo) doses taken to treat an individual HAE attack or taken within a 24-hour period. For convenience, exposure and exposure period are used interchangeably in the overview of safety.

Overall, sebetralstat is well tolerated and has an acceptable, consistent, and well characterized safety profile. The safety profile in patients with HAE in the Phase 2 and 3 trials is consistent

with that observed in healthy subjects in the Phase 1 trials. The safety profile in pediatric patients (12 years and over) is consistent with that observed in adult patients.

Demographics and Baseline Characteristics

In the Phase 2-3 trials (within the All-Subjects Safety Population), mean (range) age was 37.0 years (13 to 77). Twenty-one patients (9.9%) were pediatrics ≥ 12 to < 18 years old; 6 patients (2.8%) were geriatrics (≥ 65 years). The majority of patients were White (86.4%); 7.0% of patients were Asian. Over half of the patients (58.7%) were female. Phase 2-3 trials were conducted in 20 countries; as of the data cutoff date (31 January 2024), patients have been dosed with the IMP in geographic regions of Europe (62.9%), North America (22.5%), Japan (4.7%), and Rest of World (comprising Australia and Israel in KVD900-301 and Australia, Israel, and South Africa in KVD900-302) (9.9%).

Overall, the trial patients were representative of the general population of patients with HAE Type I or II (91.8% with Type I and 8.2% with Type II in the pivotal efficacy trial KVD900-301). In KVD900-301 and KVD900-302, the trial populations included 178 patients who entered the trial taking only conventional on-demand treatment and 35 patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment (including berotralstat, lanadelumab, and C1-INH). All Phase 2-3 trials enrolled a geographically and racially representative sample.

In Phase 1 trials, mean age was 39.3 years (19 to 68). The majority of subjects were White (69.4%), 16.4% of subjects were Black or African American, and 12% of subjects were Asian. Phase 1 trials were conducted in the United States (81.6% of subjects) and United Kingdom (18.4% of subjects).

Patient exposure

For this marketing application, as of the data cutoff date (31 January 2024) the clinical development program has included 670 unique participants who received at least one administration of IMP (sebetralstat, placebo, and/or DDI co-medications). A total of 213 were patients in Phase 2-3 trials and 457 were healthy subjects in Phase 1 trials (129 in DDI trials and 328 in non-DDI trials). Of the 213 patients in Phase 2-3, 208 have received at least one administration of sebetralstat to date. This includes 10 patients who received sebetralstat as part of the safety and PK evaluation in Part 1 of KVD900-201 and did not treat any attacks with sebetralstat in Part 2. In total, 198 patients in Phase 2-3 trials have treated 879 attacks with sebetralstat; this includes 21 paediatric patients (age ≥ 12 to < 18 years) who treated 159 attacks and 5 geriatric patients (age ≥ 65 years) who treated 27 attacks with sebetralstat.

Of the 670 participants in the All-Subjects Safety Population, 575 (85.8%) received a total of 1,970 administrations of sebetralstat ≥ 300 mg and 537 (80.1%) received 1,829 administrations of sebetralstat ≥ 600 mg.

In the pivotal KVD900-301 trial, paediatric patients (n=13) received a total of 10 administrations of 300 mg and 11 administrations of 600 mg (9 administrations of placebo). The intended commercial patient population (adults and paediatrics 12 years and over) was included in the pivotal trials; as such, the safety database has no limitations and is considered adequate to support the proposed label.

In the Phase 2 and 3 Double-blind Safety Population, the majority of attacks were treated with a single administration (300 mg: 66.3%; 600 mg: 77.1%; placebo: 71.7%). In KVD900-301, if needed (as determined by the patient), a second administration of the same assigned treatment could have been taken for each attack. A second administration was used for the remaining attacks (300 mg: 33.7%; 600 mg: 22.9%; placebo: 28.3%). Note that only a single administration of 600 mg sebetralstat was allowed in KVD900-201.

In the Phase 2 and 3 Treated Safety Population, the mean (SD) number of administrations was 1.3 (0.56), 1.4 (0.63), and 1.5 (0.75) for the 3rd through 5th attacks, noting that the 1st and 2nd attacks in the pooled analysis table included patients who were enrolled in KVD900-201, for whom only a single administration of 600 mg sebetralstat was allowed thus impacting the means for those attack numbers. Overall, the percentage of attacks treated with 2 or more administrations remained stable and did not increase with more treatment exposures over time. Of the 80 total attacks treated with at least 2 administrations to treat an attack, the majority (92.7%) were treated with exactly 2.

In the long-term open-label trial KVD900-302, not counting use for short-term prophylaxis, 10 of the 84 patients (11.9%) have treated a total of 18 attacks (2.8% of 640 attacks) with 3 administrations of sebetralstat, as of the 31 January 2024 data cutoff date.

In KVD900-302, the median number of months for patients to be enrolled to date was 3.21 months (range: 0.3 to 13.5). Forty-five patients (53.6%) have been enrolled for at least 3 months, 22 patients (26.2%) for at least 6 months, and 3 patients (3.6%) for at least 12 months. The median number of the IMP treated attacks was 5. The median IMP dosing frequency (administrations/month) was 2.2 (range: 0.3 to 7.9). The maximum number of attacks treated by a single patient in KVD900-302 over the duration of the trial was 37; the maximum number of administrations taken by this patient over the total duration of the trial was 56. Thirty-three patients (39.3%) have treated more than 5 attacks.

Overview of Adverse Events

Phase 2-3

Overall, the type and incidence of TEAEs were similar following treatment with sebetralstat compared with placebo.

In the Phase 2-3 Double-Blind Safety Population, 17/86 patients (19.8%) who received 300 mg reported a total of 20 TEAEs (1.30 events per patient-year); 28/151 patients (18.5%) who received 600 mg reported a total of 39 TEAEs (1.58 events per patient-year), and 24/138 patients (17.4%) who received placebo reported a total of 34 TEAEs (1.68 events per patient-year).

The only TEAE reported by $\geq 2\%$ of patients in any treatment group was headache (1 patient [1.2%] who received 300 mg, 7 patients [4.6%] who received 600 mg, and 4 patients [2.9%] who received placebo). For the event of headache, the risk difference (95% CI) for 300 mg or 600 mg versus placebo was -1.2% (-4.5, 2.0) and 1.8% (-2.6, 6.1), respectively.

The only on-treatment TEAE (occurring within 3 days after IMP administration) reported for $\geq 2\%$ of patients in any treatment group was headache (6 patients [4.0%] who received 600 mg and 3 patients [2.2%] who received placebo). On-treatment TEAEs were similar following treatment with sebetralstat compared with placebo.

The majority of TEAEs were mild or moderate in severity, and there were no trends between sebetralstat versus placebo in the severity of reported events. There were no apparent dose-related increases in the severity or frequency of TEAEs, and no apparent trends in frequency or severity of TEAEs based on number of treatment administrations or exposures.

In the Phase 2-3 Double-blind Safety Population, the majority of TEAEs were considered by Investigators to be not related to the IMP, and IMP-related TEAEs were similar following treatment with sebetralstat compared with placebo. The only IMP-related TEAE reported by more than a single patient in any treatment group was headache (2 patients [1.3%] who received 600 mg and 2 patients [1.4%] who received placebo). All other IMP-related TEAEs were each experienced by a single patient.

Safety findings in the Phase 2 and 3 Treated Safety Population were similar to the Phase 2 and 3 Double-blind Safety Population. In both the Phase 2 and 3 Treated Safety Population and the Phase 3 Second-administration Safety Population, there were no trends in events per patient-year based on exposure number for the treatment period or the on-treatment period. The TEAE profile of sebetralstat was generally similar across all subgroups analyzed, including age group and geographic region.

Phase 1

In the Phase 1 Non-DDI Safety Population, TEAEs were reported for 8 subjects (18.2%) who received <300 mg sebetralstat (8 total events; 6.40 events per subject-year), 1 subject (3.8%) who received 300 mg sebetralstat (1 event; 1.96 events per subject-year), 29 subjects (22.7%) who received 600 mg sebetralstat or equivalent (60 total events, 10.73 events per subject-year), 15 subjects (17.9%) who received >600 mg sebetralstat (27 total events; 13.50 events per subject-year), and 10 subjects (13.5%) who received placebo (13 total events; 7.39 events per subject-year).

Key safety findings were as follows:

- The most frequently reported TEAEs in Phase 1 were similar to Phase 2 and 3
- The only TEAE reported for $\geq 5\%$ of subjects in any treatment group in the Phase 1
-
- Non-DDI Safety Population was headache
- Headache was the only TEAE reported for $\geq 5\%$ of subjects in any treatment group that was considered by the investigator to be related to the IMP
- All TEAEs were mild or moderate in severity, with no severe events reported
- No SAEs or TEAEs leading to trial discontinuation were reported

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred while on trial.

Across the clinical development program, 6 patients reported a total of 8 treatment-emergent SAEs. None occurred within 3 days of IMP administration (i.e. on-treatment), and none were considered by the investigator to be related to the IMP.

A total of 6 patients with HAE or healthy subjects in sebetralstat treatment groups reported TEAEs leading to trial discontinuation and/or withdrawal of the IMP, including 4 patients in KVD900-302 and 2 healthy subjects in Phase 1 DDI trials:

- In KVD900-302, one of the TEAEs leading to trial discontinuation was also an SAE (intracranial mass, considered not related to IMP). Two TEAEs leading to trial discontinuation occurred on-treatment (i.e. within 3 days after IMP administration) and were considered by the investigator to be related to the IMP (events of skin burning sensation and nausea); both of these events resolved without intervention. The remaining TEAE leading to trial discontinuation in KVD900-302 was an event of ALT increased that occurred subsequent to an SAE of viral meningitis; the event was considered not related to IMP.
- In the Phase 1 trials, TEAEs leading to discontinuation from the trial or withdrawal of the IMP were reported by 1 healthy subject in KVD900-106 (event of AST increased) and 1 healthy subject in KVD900-112 (event of COVID-19). The event of AST increased (1.06 x ULN) occurred within 3 days of administration of sebetralstat alone (i.e. was on-treatment), was transient, mild in severity, non-serious and did not require treatment. The AST values increased further to 1.75 x ULN 3 days later, after administration of 2 doses of co administrator itraconazole (200 mg) alone. The event was considered related to sebetralstat and itraconazole. The event of COVID-19 was considered not related to the IMP. Both events resolved during the respective trial

No other TEAEs of significance have occurred.

There were no AEs of special interest, and no meaningful trends were identified after review of the safety data; therefore, Standardized MedDRA Queries were not run.

Due to the critical nature of laryngeal attacks, the safety profile following laryngeal attacks was examined in an ad hoc analysis. There were no notable safety findings, including no events of dysphagia and no on-treatment events (i.e. that occurred within 3 days after IMP administration), following laryngeal attacks.

No SAEs were considered related to sebetralstat, and therefore, no serious adverse reactions or suspected unexpected serious adverse reactions (SUSARs) have been reported across the program.

Overall, the majority of TEAEs in Phase 2-3 were considered by investigators to be not related to IMP. There were no patterns or discernible trends in frequency or severity of IMP-related TEAEs following treatment with sebetralstat compared with placebo.

Adverse Drug Reactions

Adverse reactions were defined as IMP-related, on-treatment (i.e. within 3 days after IMP administration) TEAEs that were observed in $\geq 1\%$ of patients in any sebetralstat group that also occurred at a higher rate than placebo.

Comments

Across all clinical phases, the safety data consistently indicate that sebetralstat is well-tolerated. TEAEs were predominantly mild or moderate, and there was no evidence of dose-related increases in frequency or severity. The consistency of the safety profile across diverse patient populations, including paediatric and geriatric groups, and different geographic regions, suggests that the drug can be safely used in its intended population.

The findings are further supported by the absence of significant safety signals, including severe TEAEs, SAEs, or discontinuations due to adverse events. Headache, the most commonly reported TEAE, was comparable in incidence to placebo and did not indicate a meaningful safety concern.

Study KVD900-301

Overall, 20 TEAEs were reported for 17 (19.8%) patients in the 300 mg KVD900 group, 18 TEAEs were reported for 14 (15.1%) patients in the 600 mg KVD900 group, and 24 TEAEs were reported for 17 (20.5%) patients in the placebo group.

Two treatment-related TEAEs were reported for 2 (2.3%) patients in the 300 mg KVD900 group, and 4 treatment-related TEAEs in 3 (3.2%) patients in the 600 mg KVD900 group, in comparison with 5 treatment-related TEAEs in 4 (4.8%) patients in the placebo group.

Three (2.7%) patients reported 3 SAEs: 1 patient in the 300 mg KVD900 group and 2 patients in the 600 mg KVD900 group. None of the SAEs were assessed by the investigator or sponsor as related to the IMP. All 3 SAEs led to hospitalization. The SAE in the 300 mg KVD900 group was also reported as a Grade 3 (severe) AE. There were no reported deaths or TEAEs leading to trial discontinuation.

Table 6. Overall Treatment-Emergent Adverse Events (Safety Set)

Number of Patients	300 mg KVD900 (N=86) n (%) E	600 mg KVD900 (N=93) n (%) E	Placebo (N=83) n (%) E
Any TEAE	17 (19.8) 20	14 (15.1) 18	17 (20.5) 24
Any related TEAE	2 (2.3) 2	3 (3.2) 4	4 (4.8) 5
Any Grade 3 or higher TEAE	1 (1.2) 1	0	0
Any related Grade 3 or higher TEAE	0	0	0
Any SAE	1 (1.2) 1	2 (2.2) 2	0
Any related SAE	0	0	0
Any TEAE leading to hospitalization	1 (1.2) 1	2 (2.2) 2	0
Any TEAE leading to trial discontinuation	0	0	0
Any TEAE leading to death	0	0	0

Notes: n represents the number of patients at each level of summarization. N is number of patients that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the IMP-treated HAE attacks.

E represents the number of events at each level of summarization.

Patient 2301305 and Patient 2901305 both treated 2 attacks with 600 mg KVD900; all Safety Set analyses were conducted per the actual treatment received.

A TEAE was defined as an AE that met any of the following conditions: (1) began on or after the first dose date of IMP, (2) began before the first dose date of IMP and increased in severity on or after the first dose date of IMP, (3) was completely missing a start date and the stop date, (4) was completely missing a start date and the stop date was on or after the first dose date of IMP.

On-treatment

Overall, 5 on-treatment TEAEs (i.e., TEAE occurring within 3 days post IMP administration) were reported for 5 (5.8%) patients in 300 mg KVD900 group, 6 on-treatment TEAEs were reported for 6 (6.5%) patients in the 600 mg KVD900 group, and 13 on-treatment TEAEs were reported for 10 (12%) patients in the placebo group; and 2 on-treatment TEAEs related to the IMP were reported for 2 (2.3%) patients in the 300 mg KVD900 group and 2 on-treatment TEAEs related to the IMP were reported for 2 (2.2%) patients in the 600 mg KVD900 group and 5 on-treatment TEAEs related to the IMP were reported for 4 (4.8%) patients in the placebo group.

Table 7. On-treatment TEAEs

Group	On-treatment TEAEs	Patients with TEAEs	TEAEs related to IMP	Patients with TEAEs related to IMP
300 mg KVD900	5	5 (5.8%)	2	2 (2.3%)
600 mg KVD900	6	6 (6.5%)	2	2 (2.2%)
Placebo	13	10 (12%)	5	4 (4.8%)

Study KVD900-201

Overall, 25/68 subjects (36.8%) experienced at least 1 TEAE. The highest proportion of subjects that experienced at least 1 TEAE was following treatment with KVD900 in Part 2 (14/58 subjects [24.1%]).

Of the 25 subjects that experienced at least 1 TEAE, 10/68 subjects (14.7%) experienced at least 1 on-treatment (occurring within 48 hours post dose) TEAE and 15/68 subjects (22.1%) experienced at least 1 post-treatment TEAE. The highest proportion of subjects that experienced at least 1 on-treatment TEAE (7/68 subjects [12.1%]) and 1 post-treatment TEAE (7/68 subjects [12.1%]) was following treatment with KVD900 in Part 2.

The majority of TEAEs (42 of 55 events [76.4%]) experienced in the study were not study drug-related while 13 of 55 events [23.6%] were study drug-related. Overall, 7/68 subjects (10.3%) experienced at least 1 drug-related TEAE. The proportion of subjects that experienced at least 1 drug-related TEAE was similar across KVD900 and placebo treatment. Overall, 1/68 subjects (1.5%) experienced 1 severe TEAE, following treatment with KVD900 in Part 1. No subject experienced a serious TEAE, a serious drug-related TEAE, a TEAE leading to withdrawal from the study or a TEAE leading to death.

Table 8. Summary of Treatment-Emergent Adverse Events (Safety Set)

	Number of Event/Subjects (%)				
	Part 1	Part 2			
	600 mg KVD900 (N=68)	600 mg KVD900 (N=58)	(Placebo) (N=55)	KVD900 Combined (N=68)	Overall (N=68)
Any TEAEs	24 / 12 (17.6%)	21 / 14 (24.1%)	10 / 7 (12.7%)	45 / 22 (32.4%)	55 / 25 (36.8%)
On-treatment TEAEs	13 / 5 (7.4%)	12 / 7 (12.1%)	7 / 4 (7.3%)	25 / 9 (13.2%)	32 / 10 (14.7%)
Post-treatment TEAEs	11 / 7 (10.3%)	9 / 7 (12.1%)	3 / 3 (5.5%)	20 / 13 (19.1%)	23 / 15 (22.1%)
Severe TEAEs	1 / 1 (1.5%)	-	-	1 / 1 (1.5%)	1 / 1 (1.5%)
Serious TEAEs	-	-	-	-	-
Drug-related TEAEs	8 / 5 (7.4%)	3 / 3 (5.2%)	2 / 2 (3.6%)	11 / 6 (8.8%)	13 / 7 (10.3%)
Serious drug-related TEAEs	-	-	-	-	-
TEAEs leading to withdrawal from the study	-	-	-	-	-
TEAEs leading to death	-	-	-	-	-

Abbreviations: TEAE=treatment-emergent adverse event

The denominator for each percentage is the number of subjects in the SAF within a treatment category.

On-treatment defined as occurring within 48 hours post-dose. Post-treatment defined as occurring >48 hours post-dose and prior to the next dose.

Study KVD900-302

Of the 84 patients in the Safety Set, 47 (56.0%) patients reported a total of 153 TEAEs. Eight (9.5%) patients reported 18 TEAEs related to the IMP. The most commonly reported ($\geq 2\%$ patients overall) TEAE related to IMP was headache (3 [3.6%] patients reporting 4 TEAEs). Twenty-six (31.0%) patients reported a total of 56 TEAEs within 3 days of IMP administration (on-treatment). Four (4.8%) patients reported TEAEs leading to study discontinuation.

Five (6.0%) patients reported 6 TEAEs (diarrhoea, meningitis viral, muscle strain and back pain [1 TEAE each]; headache [2 TEAEs]) of Grade 3 severity, of which only 1 TEAE (diarrhoea) was IMP-related.

Overall, 3 (3.6%) patients reported 5 serious TEAEs (hyperthermia, meningitis viral, Waldenstrom's macroglobulinemia, intracranial mass and headache), of which 2 patients reported 4 serious TEAEs leading to hospitalization. None of the serious TEAEs were IMP-related.

There were no TEAEs leading to death in the trial.

Table 9. Overall Treatment-Emergent Adverse Events (Safety Set)

Number of Patients with	Rollover (N=50) n (%) E	Non-Rollover (N=34) n (%) E	Total (N=84) n (%) E
Any TEAE	30 (60.0) 106	17 (50.0) 47	47 (56.0) 153
Any related TEAE	4 (8.0) 8	4 (11.8) 10	8 (9.5) 18
Any TEAE within 3 days of IMP administration	14 (28.0) 35	12 (35.3) 21	26 (31.0) 56
Any Grade 3 or higher TEAE	3 (6.0) 4	2 (5.9) 2	5 (6.0) 6
Any related Grade 3 or higher TEAE	0	1 (2.9) 1	1 (1.2) 1
Any serious TEAE	2 (4.0) 4	1 (2.9) 1	3 (3.6) 5
Any related serious TEAE	0	0	0
Any TEAE leading to hospitalization	2 (4.0) 4	0	2 (2.4) 4
Any TEAE leading to trial discontinuation	3 (6.0) 3	1 (2.9) 1	4 (4.8) 4
Any TEAE leading to death	0	0	0

Note: n represents the number of patients at each level of summarization.

E represents the number of adverse events at each level of summarization.

A TEAE was defined as an AE that met any of the following conditions: (1) began on or after the first IMP dose date, (2) began before the first IMP dose date and increased in severity on or after the first IMP dose date, (3) was completely missing a start date and a stop date, (4) was completely missing a start date and the stop date was on or after the first IMP dose date.

Adverse events were coded using MedDRA, Version 26.0.

Most common adverse events

Phase 2-3

Overall, the type and frequency of TEAEs were similar following treatment with sebetralstat compared with placebo. The only TEAE reported by $\geq 2\%$ of patients in any treatment group were headache (1 patient [1.2%] who received 300 mg, 7 patients [4.6%] who received 600 mg, and 4 patients [2.9%] who received placebo). For the event of headache, the risk difference (95% CI) for 300 mg or 600 mg versus placebo was -1.2% (-4.5, 2.0) and 1.8% (-2.6, 6.1), respectively.

Table 10. Phase 2 and 3 Double-blind Safety Population: Summary of Treatment-Emergent Adverse Events Reported by $\geq 2\%$ of Patients in Any Treatment Group by Preferred Term

System Organ Class Preferred Term	Sebetralstat 300 mg (N=86) n (%) m	Sebetralstat 600 mg (N=151) n (%) m	Placebo (N=138) n (%) m
Any TEAE	17 (19.8) 20	28 (18.5) 39	24 (17.4) 34
Headache	1 (1.2) 1	7 (4.6) 7	4 (2.9) 4

n = number of patients experiencing the event, m = number of events

The Phase 2 and 3 Double-blind Safety Population included all randomized and treated patients from Phase 2 and 3 trials KVD900-201 and KVD900-301, respectively, during the double-blind treatment period

MedDRA Dictionary (Version 26.0) was used for coding AEs
System Organ Class terms are sorted using alphabetical order

Phase 1

The only TEAE reported for $\geq 5\%$ of subjects in any treatment group in the Phase 1 Non-DDI Safety Population was headache (1 subject [2.3%] who received <300 mg, 8 subjects [6.3%] who received 600 mg or equivalent, 8 subjects [9.5%] who received >600 mg, and 2 subjects [2.7%] who received placebo).

The 95% CI risk differences between all sebetralstat dose levels versus placebo contained 0 for all event terms except for headache in subjects who received sebetralstat 600 mg or equivalent (risk difference [95% CI] 15.5% (2.1, 28.9)). Note: further evaluation was undertaken in an ad hoc analysis that summarized overall TEAEs for subjects in the placebo-controlled Phase 1 non-DDI trials only; this analysis showed that when only the controlled

trials were included, the 95% CI for risk difference contained 0 for headache events in subjects who received 600 mg or equivalent (risk difference [95% CI] 8.4% [-5.1, 21.8]).

Table 11. Phase 1 Non-DDI Safety Population: Summary of Treatment-Emergent Adverse Events Reported by $\geq 5\%$ of Healthy Subjects in Any Treatment Group by Preferred Term

System Organ Class Preferred Term	Sebetralstat <300 mg (N=44) n (%) m	Sebetralstat 300 mg (N=26) n (%) m	Sebetralstat 600 mg or equivalent (N=128) n (%) m	Sebetralstat >600 mg (N=84) n (%) m	Placebo (N=74) n (%) m
Any TEAE	8 (18.2) 8	1 (3.8) 1	29 (22.7) 50	15 (17.9) 27	10 (13.5) 13
Headache	1 (2.3) 1	0	8 (6.3) 9	8 (9.5) 8	2 (2.7) 2

n = number of subjects experiencing the event. m = number of events

Notes: The Phase 1 Non-DDI Safety Population included all treated subjects from Phase 1 trials KVD900-101, KVD900-102, KVD900-103, KVD900-104, KVD900-107, KVD900-108, KVD900-109, and KVD900-110

MedDRA Dictionary (Version 28.0) was used for coding AEs

System Organ Class terms are sorted using alphabetical order

Based on logical groupings of TEAE preferred terms, the grouped TEAEs observed in $\geq 5\%$ of subjects in any treatment group were upper respiratory tract infection (3 subjects [6.8%] who received <300 mg sebetralstat and 1 [0.8%] subject who received the 600 mg or equivalent) and headache (1 subjects [2.3%] who received <300 mg, 8 subjects [6.3%] who received 600 mg or equivalent, 8 subjects [9.5%] who received >600 mg, and 2 subjects [2.7%] who received placebo).

On-treatment Adverse Events

Phase 2-3

Overall, the type and frequency of on-treatment TEAEs (occurring within 3 days after IMP administration) were similar following treatment with sebetralstat compared with placebo. In the Phase 2 and 3 Double-blind Safety Population (ISS Table 13.3.1), the only on-treatment TEAE reported for $\geq 2\%$ of patients in any treatment group was headache (6 patients [4.0%] who received 600 mg and 3 patients [2.2%] who received placebo).

The 95% CI for risk differences between 300 mg or 600 mg sebetralstat versus placebo contained 0 for all on-treatment TEAEs reported for $\geq 2\%$ of patients in any treatment group. Based on logical groupings of on-treatment TEAE preferred terms, the grouped on-treatment TEAEs observed in $\geq 2\%$ of patients in any treatment group were upper respiratory tract infection (1 patient [1.2%] who received 300 mg, 0 patients who received 600 mg, and 4 patients [2.9%] who received placebo) and headache (0 patients who received 300 mg, 6 patients [4.0%] who received 600 mg, and 3 patients [2.2%] who received placebo)

Phase 1

In the Phase 1 Non-DDI Safety Population, headache was the only on-treatment TEAE (occurring within 3 days after IMP administration) reported for $\geq 5\%$ of subjects in any treatment group (1 subject [2.3%] who received <300 mg, 7 subjects [5.5%] who received 600 mg, 8 subjects [9.5%] who received >600 mg, and 2 subjects [2.7%] who received placebo).

Based on logical groupings of TEAE preferred terms, the grouped on-treatment TEAEs observed in $\geq 5\%$ of subjects in any treatment group were upper respiratory tract infection (3 subjects [6.8%] who received <300 mg sebetralstat, 1 subject [0.8%] who received 600 mg or equivalent, and no subjects in any other treatment group) and headache (1 subject [2.3%] who received <300 mg, 7 subjects [5.5%] who received 600 mg or equivalent, 8 subjects [9.5%] who received >600 mg, and 2 subjects [2.7%] who received placebo)

Comment

The overall safety profile of sebetralstat appears acceptable, with no major safety signals identified. The most commonly reported TEAE across all studies was headache, which occurred at a slightly higher frequency in the 600 mg group compared to placebo. This difference, while measurable, did not appear to represent a clinically significant safety concern. The incidence of upper respiratory tract infections was low and consistent with expected rates in the study population.

There were no notable imbalances or concerning trends in TEAEs, including on-treatment events, suggesting that sebetralstat is well-tolerated at the studied doses. Further monitoring may be warranted for headache at higher doses, but overall, these data support the continued clinical development of sebetralstat.

Study KVD900-301

The most common TEAEs (i.e., TEAEs that occurred in more than 2% of patients[3 or more, regardless of treatment group]) reported by preferred term included headache (4 [3.4%] patients in the 600 mg KVD900 group, and 1 [1.2%] patient each in 300 mg KVD900 and placebo groups), and vomiting (1 [1.1%] patient in the 600 mg KVD900 group and 1 [1.2%] patient each in 300 mg KVD900 and placebo groups). All other TEAE occurrences were reported in 1 patient in any given treatment group.

Table 12. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	300 mg KVD900 (N=86) n (%) E	600 mg KVD900 (N=93) n (%) E	Placebo (N=83) n (%) E
Total number of TEAEs	17 (19.8) 20	14 (15.1) 18	17 (20.5) 24
Congenital, familial, and genetic disorders	0	1 (1.1) 1	0
Hereditary angioedema	0	1 (1.1) 1	0
Eye disorders	0	1 (1.1) 1	1 (1.2) 1
Anisocoria	0	1 (1.1) 1	0
Eye haemorrhage	0	0	1 (1.2) 1
Gastrointestinal disorders	4 (4.7) 4	4 (4.3) 4	4 (4.8) 4
Vomiting	1 (1.2) 1	1 (1.1) 1	1 (1.2) 1
Abdominal pain	0	1 (1.1) 1	1 (1.2) 1
Dyspepsia	1 (1.2) 1	1 (1.1) 1	0
Nausea	0	1 (1.1) 1	1 (1.2) 1
Dental caries	1 (1.2) 1	0	0
Gingival bleeding	1 (1.2) 1	0	0
Toothache	0	0	1 (1.2) 1
General disorders and administration site conditions	1 (1.2) 1	0	1 (1.2) 1
Fatigue	1 (1.2) 1	0	1 (1.2) 1
Immune system disorders	1 (1.2) 1	0	0
Seasonal allergy	1 (1.2) 1	0	0
Infections and infestations	4 (4.7) 4	2 (2.2) 2	5 (6.0) 5
COVID-19	1 (1.2) 1	1 (1.1) 1	0
Fungal skin infection	1 (1.2) 1	0	0
Influenza	0	0	1 (1.2) 1
Laryngitis	1 (1.2) 1	0	0
Localised infection	0	0	1 (1.2) 1
Pharyngitis	0	0	1 (1.2) 1
Pharyngitis bacterial	0	0	1 (1.2) 1
Pharyngitis streptococcal	1 (1.2) 1	0	0
Upper respiratory tract infection	0	1 (1.1) 1	0
Viral upper respiratory tract infection	0	0	1 (1.2) 1
Investigations	2 (2.3) 5	2 (2.2) 2	2 (2.4) 2
Alanine aminotransferase increased	0	0	1 (1.2) 1
Albumin urine present	1 (1.2) 1	0	0
Blood glucose increased	0	1 (1.1) 1	0
Blood triglycerides increased	1 (1.2) 1	0	0
Blood urine present	1 (1.2) 1	0	0
Gamma-glutamyltransferase increased	0	1 (1.1) 1	0
Glucose urine present	1 (1.2) 1	0	0
Mean cell volume increased	1 (1.2) 1	0	0
Weight decreased	0	0	1 (1.2) 1
Musculoskeletal and connective tissue disorders	2 (2.3) 2	0	1 (1.2) 1
Intervertebral disc protrusion	1 (1.2) 1	0	0

System Organ Class Preferred Term	300 mg KVD900 (N=86) n (%) E	600 mg KVD900 (N=93) n (%) E	Placebo (N=83) n (%) E
Neck pain	0	0	1 (1.2) 1
Pain in extremity	1 (1.2) 1	0	0
Nervous system disorders	1 (1.2) 1	5 (5.4) 5	3 (3.6) 3
Headache	1 (1.2) 1	4 (4.3) 4	1 (1.2) 1
Amnesia	0	0	1 (1.2) 1
Dizziness	0	1 (1.1) 1	0
Dysgeusia	0	0	1 (1.2) 1
Psychiatric disorders	1 (1.2) 1	0	0
Attention deficit hyperactivity disorder	1 (1.2) 1	0	0
Renal and urinary disorders	0	0	1 (1.2) 1
Albuminuria	0	0	1 (1.2) 1
Reproductive system and breast disorders	0	1 (1.1) 1	2 (2.4) 2
Menstruation irregular	0	0	2 (2.4) 2
Menopausal symptoms	0	1 (1.1) 1	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.2) 1
Epistaxis	0	0	1 (1.2) 1
Skin and subcutaneous tissue disorders	1 (1.2) 1	1 (1.1) 1	2 (2.4) 3
Acne conglobata	0	0	1 (1.2) 1
Eczema	0	0	1 (1.2) 1
Hand dermatitis	1 (1.2) 1	0	0
Psoriasis	0	1 (1.1) 1	0
Rash	0	0	1 (1.2) 1
Vascular disorders	0	1 (1.1) 1	0
Hot flush	0	1 (1.1) 1	0

Notes: At each level of patient summarization, a patient was counted once if the patient reported 1 or more events.

n represents the number of patients at each level of summarization. N is number of patients randomized using a permuted-block randomization method to ensure a balanced assignment to each of the 6 treatment sequences, to receive that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the analyzed IMP-treated HAE attacks, according to the actual treatment received.

[E] represents the number of events at each level of summarization.

Adverse events were coded using MedDRA, Version 26.0.

Source: Table 14.3.1.2.1.

On-treatment

Overall, on-treatment TEAEs were more frequently reported in the SOC of gastrointestinal disorders (3 on-treatment TEAEs reported for 3 [3.5%] patients in 300 mg KVD900 group, 2 on-treatment TEAEs reported for 2 [2.2%] patients in 600 mg KVD900 group, and 3 on-treatment TEAEs reported for 3 [3.6%] patients in placebo group) and nervous system disorders (4 on-treatment TEAEs reported for 4 [4.3%] patients in 600 mg KVD900 group and 2 on-treatment TEAEs reported for 2 [2.4%] patients in placebo group).

Table 13. Most frequent SOC for On-treatment TEAEs

SOC	Group	On-treatment TEAEs	Patients	Percentage
Gastrointestinal disorders	300 mg KVD900	3	3	3.5%
Gastrointestinal disorders	600 mg KVD900	2	2	2.2%
Gastrointestinal disorders	Placebo	3	3	3.6%
Nervous system disorders	600 mg KVD900	4	4	4.3%

Nervous system disorders	Placebo	2	2	2.4%
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The most common on-treatment TEAEs (i.e., TEAEs that occurred in more than 2% of patients [3 or more, regardless of treatment group]) reported by preferred term were headache (3 on-treatment TEAEs reported for 3 [3.2%] patients in the 600 mg KVD900 group and 1 on-treatment TEAE reported for 1 [1.2%] patient in the placebo group) and vomiting (1 on-treatment TEAE each reported for 1 [1.2%] patient each in 300 mg KVD900 group and placebo group and 1 [1.1%] patient in the 600 mg KVD900 group).

Table 14. Most common PT for On-treatment TEAEs

TEAE	600 mg KVD900	300 mg KVD900	Placebo
Headache	3 (3.2%)	0	1 (1.2%)
Vomiting	1 (1.1%)	1 (1.2%)	1 (1.2%)

Study KVD900-201

Overall, 25/68 subjects (36.8%) experienced at least 1 TEAE (see Section 12.2.1). The majority of TEAEs were experienced by 1 subject each.

Overall, the most common* TEAE SOC were:

Infections and infestations (14.7%);

Gastrointestinal disorders (10.3%).

*Occurring in $\geq 10\%$ of overall subjects.#

Overall, the most common# TEAE PTs were:

8 events of headache experienced by 5 subjects (7.4%);

4 events of nasopharyngitis experienced by 4 subjects (5.9%).

#Occurring in $\geq 5\%$ of overall subjects.

The incidence of headache and nasopharyngitis was similar following treatment with KVD900 or placebo.

There was no clear pattern or discernible trends in TEAEs following treatment with KVD900 or placebo.

Study KVD900-302

The TEAEs were most commonly ($\geq 5\%$ patients overall) reported in the SOC of gastrointestinal disorders (9 [10.7%] patients), infections and infestations (34 [40.5%] patients), investigations (5 [6.0%] patients), nervous system disorders (13 [15.5%] patients), and skin and subcutaneous tissue disorders (7 [8.3%] patients).

Most TEAEs were reported in one (1.2%) patient overall. The TEAEs reported in $\geq 2\%$ patients overall were headache (10 [11.9%] patients); nasopharyngitis and upper respiratory tract infection (each in 7 [8.3%] patients); COVID-19 and viral upper respiratory tract infection (each in 4 [4.8%] patients); vomiting, influenza, urinary tract infection (each in 3 [3.6%] patients), and diarrhea, seasonal allergy, gastroenteritis, gastroenteritis viral, alanine aminotransferase increased, aspartate aminotransferase increased, back pain, migraine, and urticaria (each in 2 [2.4%] patients). Two (2.4%) patients reported 2 uncoded TEAEs (these terms remained uncoded because the data included in this CSR was up to 31 Jan 2024, only the data up to 15 Dec 2023 was cleaned).

Table 15. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by $\geq 2\%$ Patients Overall (Safety Set)

System Organ Class Preferred Term	Rollover (N=50) n (%) E	Non-Rollover (N=34) n (%) E	Total (N=84) n (%) E
All treatment-emergent adverse events	30 (60.0) 106	17 (50.0) 47	47 (56.0) 153
Gastrointestinal disorders			
Vomiting	1 (2.0) 1	2 (5.9) 4	3 (3.6) 5
Diarrhea	1 (2.0) 1	1 (2.9) 5	2 (2.4) 6
Immune system disorders			
Seasonal allergy	2 (4.0) 2	0	2 (2.4) 2
Infections and infestations			
Nasopharyngitis	5 (10.0) 7	2 (5.9) 3	7 (8.3) 10
Upper respiratory tract infection	5 (10.0) 5	2 (5.9) 2	7 (8.3) 7
COVID-19	3 (6.0) 3	1 (2.9) 1	4 (4.8) 4
Viral upper respiratory tract infection	2 (4.0) 2	2 (5.9) 2	4 (4.8) 4
Influenza	2 (4.0) 2	1 (2.9) 1	3 (3.6) 3
Urinary tract infection	2 (4.0) 2	1 (2.9) 1	3 (3.6) 3
Gastroenteritis	1 (2.0) 1	1 (2.9) 1	2 (2.4) 2
Gastroenteritis viral	1 (2.0) 1	1 (2.9) 1	2 (2.4) 2
Investigations			
Alanine aminotransferase increased	2 (4.0) 2	0	2 (2.4) 2
Aspartate aminotransferase increased	2 (4.0) 2	0	2 (2.4) 2
Musculoskeletal and connective tissue disorders			
Back pain	2 (4.0) 4	0	2 (2.4) 4
Nervous system disorders			
Headache	5 (10.0) 13	5 (14.7) 7	10 (11.9) 20
Migraine	2 (4.0) 2	0	2 (2.4) 2
Skin and subcutaneous tissue disorders			
Urticaria	1 (2.0) 2	1 (2.9) 1	2 (2.4) 3
Uncoded	1 (2.0) 1	1 (2.9) 1	2 (2.4) 2 ^a

Note: At each level of patient summarization, a patient was counted once if the patient reported one or more events.

N represents the number of patients at each level of summarization.

E represents the number of adverse events at each level of summarization.

Adverse events were coded using MedDRA, Version 26.0.

^a Uncoded terms were due to the data included in this CSR up to 31 Jan 2024, only the data up to 15 Dec 2023 was cleaned

Common on-treatment TEAEs

The on-treatment TEAEs were most commonly (>5% patients overall) reported in the SOC of infections and infestations (13 [15.5%] patients), nervous system disorders (7 [8.3%] patients), and skin and subcutaneous disorders (5 [6.0%] patients).

The on-treatment TEAEs reported most frequently (≥2% patients overall) by PTs were, headache (in 6 [7.1%] patients; vomiting gastroenteritis, influenza, nasopharyngitis (in 2 [2.4%] patients).

Adverse events by maximum intensity**Phase 2-3**

In the Phase 2 and 3 Double-blind Safety Population, almost all TEAEs were mild or moderate in severity: 1 patient (1.2%) (who received 300 mg) reported 1 severe (Grade 3) event of intervertebral disc protrusion, which did not occur on-treatment, was considered not related to IMP, and was also an SAE.

Phase 1

In the Phase 1 Non-DDI Safety Population, all TEAEs were mild or moderate in severity, with no severe events reported.

Comments

In the Phase 2-3 clinical trials, nearly all treatment-emergent adverse events (TEAEs) were of mild or moderate intensity. Only one patient (1.2%) in the 300 mg sebetralstat group reported a severe (Grade 3) TEAE of intervertebral disc protrusion. Importantly, this event was neither on-treatment nor considered related to the investigational medicinal product (IMP). The severity distribution suggests a favorable tolerability profile for sebetralstat, with no evidence of a significant burden of severe events.

In the Phase 1 Non-DDI studies, all reported TEAEs were classified as mild or moderate in severity, with no severe events observed. This further supports the conclusion that sebetralstat is well-tolerated across varying doses in healthy volunteers and patients with hereditary angioedema (HAE).

Study KVD900-301

The most common moderate TEAEs (i.e., TEAEs that occurred in more than 2% of patients, [3 or more, regardless of treatment group]) reported by preferred term were headache (4 patients in the 600 mg KVD900 group and 1 patient each in the 300 mg KVD900 and placebo groups), vomiting (1 patient each in both KVD900 and placebo treatment groups), and COVID-19 (1 patient each in 300 mg KVD900 and 600 mg KVD900 groups). The severe TEAE of intervertebral disc protrusion, reported in 1 patient in the 300 mg KVD900 group was also reported as an SAE.

Table 16. Treatment-Emergent Adverse Events by Severity Grade (Safety Set)

	300 mg KVD900	600 mg KVD900	Placebo
System Organ Class	(N=86)	(N=93)	(N=83)
Preferred Term	n (%)	n (%)	n (%)
Severity			
Total number of TEAEs	20	18	24
Grade 1 (mild)	6	6	12
Grade 2 (moderate)	13	12	12
Grade 3 (severe)	1	0	0
Number of patients with at least 1 TEAE	17 (19.8)	14 (15.1)	17 (20.5)
Grade 1 (mild)	4 (4.7)	5 (5.4)	9 (10.8)
Grade 2 (moderate)	12 (14.0)	9 (9.7)	8 (9.6)
Grade 3 (severe)	1 (1.2)	0	0
Infection and infestations	4 (4.7)	2 (2.2)	5 (6.0)
Grade 1 (mild)	1 (1.2)	1 (1.1)	3 (3.6)
Grade 2 (moderate)	3 (3.5)	1 (1.1)	2 (2.4)
Grade 3 (severe)	0	0	0
COVID-19	1 (1.2)	1 (1.1)	0
Grade 1 (mild)	0	0	0
Grade 2 (moderate)	1 (1.2)	1 (1.1)	0
Grade 3 (severe)	0	0	0
Gastrointestinal disorders	4 (4.7)	4 (4.3)	4 (4.8)
	300 mg KVD900	600 mg KVD900	Placebo
System Organ Class	(N=86)	(N=93)	(N=83)
Preferred Term	n (%)	n (%)	n (%)
Severity			
Grade 1 (mild)	0	1 (1.1)	0
Grade 2 (moderate)	4 (4.7)	3 (3.2)	4 (4.8)
Grade 3 (severe)	0	0	0
Vomiting	1 (1.2)	1 (1.1)	1 (1.2)
Grade 1 (mild)	0	0	0
Grade 2 (moderate)	1 (1.2)	1 (1.1)	1 (1.2)
Grade 3 (severe)	0	0	0
Nervous system disorders	1 (1.2)	5 (5.4)	3 (3.6)
Grade 1 (mild)	0	2 (2.2)	2 (2.4)
Grade 2 (moderate)	1 (1.2)	3 (3.2)	1 (1.2)
Grade 3 (severe)	0	0	0
Headache	1 (1.2)	4 (4.3)	1 (1.2)
Grade 1 (mild)	0	1 (1.1)	0
Grade 2 (moderate)	1 (1.2)	3 (3.2)	1 (1.2)
Grade 3 (severe)	0	0	0
Musculoskeletal and connective tissue disorders	2 (2.3)	0	1 (1.2)
Grade 1 (mild)	1 (1.2)	0	1 (1.2)
Grade 2 (moderate)	0	0	0
Grade 3 (severe)	1 (1.2)	0	0
Intervertebral disc protrusion	1 (1.2)	0	0
Grade 1 (mild)	0	0	0
Grade 2 (moderate)	0	0	0
Grade 3 (severe)	1 (1.2)	0	0

Notes: The total number of AEs counts all TEAEs for patients.

At each level of patient summarization, a patient was counted once for the maximum severity grade if the patient reported 1 or more events. N is number of patients randomized using a permuted-block randomization method to ensure a balanced assignment to each of the 6 treatment sequences, to receive that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the analyzed IMP-treated HAE attacks, according to the actual treatment received. n represents the number of patients at each level of summarization.

Adverse events were coded using MedDRA, Version 26.0.

Source: [Table 14.3.1.2.2](#).

On-treatment

Overall, on-treatment TEAEs were mild and moderate in severity. There were 2 on-treatment TEAEs reported for 2 (2.3%) patients in the 300 mg KVD900 group, 3 on-treatment TEAEs reported for 3 (3.2%) patients in the 600 mg KVD900 group, and 7 on-treatment TEAEs reported for 7 (8/4%) patients in the placebo group that reported on-treatment TEAEs of mild severity. Three on-treatment TEAEs were reported for 3 (3.5%) patients in the 300 mg KVD900 group, 3 on-treatment TEAEs reported for 3 (3.2%) patients in the 600 mg KVD900 group, and 6 on-treatment TEAEs reported of 3 (3.6%) patients in the placebo group that reported on-treatment TEAEs of moderate severity. The most common on-treatment TEAEs of moderate severity reported by preferred term were headache (2 [2.2%] patients in 600 mg KVD900 group and 1 [1.2%] patient in the placebo group) and vomiting (1 [1.2%] patient each in 300 mg KVD900 and placebo groups and 1 [1.1%] patient 600 mg KVD900 group). All other on-treatment TEAEs of mild severity were reported in 1 patient overall.

Study KVD900-201

TEAEs by maximum severity

Overall, 13/68 subjects (19.1%) experienced at least 1 mild TEAE, but no moderate or severe TEAEs, 11/68 subjects (16.2%) experienced at least 1 moderate TEAE and 1/68 subjects (1.5%) experienced 1 severe TEAE. One (1) subject in Part 1 experienced 1 TEAE of pollakiuria that was severe following treatment with KVD900 (Table 14.3.1.10). The TEAE of pollakiuria was not study drug related.

Study drug-related TEAEs by Maximum severity

Overall, 4/68 subjects (5.9%) experienced at least 1 mild study drug-related TEAE, but no moderate or severe study drug-related TEAEs, 3/68 subjects (4.4%) experienced at least 1 moderate study drug TEAE and no subject experienced a severe study drug-related TEAE. One (1) subject in Part 1 experienced moderate study drug-related dizziness, 1 subject following treatment with KVD900 in Part 2 experienced moderate study drug-related abdominal pain upper and 1 subject following treatment with placebo in Part 2 experienced moderate anal incontinence.

Study KVD900-302

Most TEAEs were of Grade 1 (68 TEAEs in 16 [19.0%] patients) or Grade 2 (79 TEAEs in 26 [31.0%] patients) severity. Grade 3 TEAEs (6 events) were reported in 5 (6.0%) patients no Grade 4 TEAEs were reported. Grade 3 TEAEs included meningitis viral, muscle strain, back pain, diarrhea (each in 1 patient), and headache (in 2 patients).

Table 17. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Severity (Safety Set)

System Organ Class Preferred Term Severity	Rollover (n=50) N (%)	Non-rollover (n=34) N (%)	Total (n=84) N (%)
Total number of treatment-emergent adverse events	106	47	153
Grade 1 (mild)	43	25	68
Grade 2 (moderate)	59	20	79
Grade 3 (severe)	4	2	6
Number of patients with at least one TEAE	30 (60.0)	17 (50.0)	47 (56.0)
Grade 1 (mild)	8 (16.0)	8 (23.5)	16 (19.0)
Grade 2 (moderate)	19 (38.0)	7 (20.6)	26 (31.0)
Grade 3 (severe)	3 (6.0)	2 (5.9)	5 (6.0)
Gastrointestinal disorders			
Diarrhea			
Grade 3 (severe)	0	1 (2.9)	1 (1.2)
Infections and infestations			
Meningitis viral			
Grade 3 (severe)	1 (2.0)	0	1 (1.2)
Injury, poisoning and procedural complications			
Muscle strain			
Grade 3 (severe)	1 (2.0)	0	1 (1.2)
Musculoskeletal and connective tissue disorders			
Back pain			
Grade 3 (severe)	1 (2.0)	0	1 (1.2)
Nervous system disorders			
Headache			
Grade 3 (severe)	1 (2.0)	1 (2.9)	2 (2.4)

Note: At each level of patient summarization, a patient was counted once for the most severe if the patient reported one or more events.

N represents the number of patients at each level of summarization.

Adverse events were coded using MedDRA, Version 26.0.

The severity of adverse events was graded using Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers.

On-demand treatment

Most on-treatment TEAEs were of Grade 1 (15 TEAEs in 8 [9.5%] patients) or Grade 2 (41 TEAEs in 18 [21.4%] patients) severity.

No Grade 3 or 4 on-treatment TEAEs were reported.

Adverse events by relationship to the IMP

Phase 2-3

Overall, the majority of TEAEs in Phase 2-3 were considered by Investigators to be not related to IMP. IMP-related TEAEs were similar following treatment with Sebetralstat compared with placebo. In the Phase 2 and 3 Double-blind Safety Population, TEAEs considered related to the IMP by the investigator were reported for 2 patients (2.3%) who received 300 mg (2 total events), 6 patients (4.0%) who received 600 mg (7 total events), and 6 patients (4.3%) who received placebo (7 total events). The only IMP-related TEAE reported by more than a single patient in any treatment group was headache (2 patients [1.3%] who received 600 mg and 2 patients [1.4%] who received placebo). All other IMP-related TEAEs were each experienced by a single patient.

Adverse reactions were defined as IMP-related, on-treatment (i.e. within 3 days after IMP administration) TEAEs that were observed in $\geq 1\%$ of patients in any sebetralstat group that also occurred at a higher rate than placebo. Adverse reactions in the KVD900-301 trial were dyspepsia and fatigue (1 patient each with 1 event).

Table 18. Phase 2 and 3 Double-blind Safety Population: Summary of IMP-related TEAEs by System Organ Class and Preferred Term

System Organ Class Preferred Term	Sebetralstat 300 mg (N=86) n (%) m	Sebetralstat 600 mg (N=151) n (%) m	Placebo (N=138) n (%) m
Any related TEAE	2 (2.3) 2	6 (4.0) 7	6 (4.3) 7
Gastrointestinal disorders	1 (1.2) 1	3 (2.0) 3	2 (1.4) 2
Dyspepsia	1 (1.2) 1	1 (0.7) 1	0
Abdominal pain upper	0	1 (0.7) 1	0
Anal incontinence	0	0	1 (0.7) 1
Nausea	0	1 (0.7) 1	1 (0.7) 1
General disorders and administration site conditions	1 (1.2) 1	0	0
Fatigue	1 (1.2) 1	0	0
Musculoskeletal and connective tissue disorders	0	1 (0.7) 1	0
Back pain	0	1 (0.7) 1	0
Nervous system disorders	0	2 (1.3) 2	3 (2.2) 3
Dysgeusia	0	0	1 (0.7) 1
Headache	0	2 (1.3) 2	2 (1.4) 2
Reproductive system and breast disorders	0	0	1 (0.7) 1
Menstruation irregular	0	0	1 (0.7) 1
Skin and subcutaneous tissue disorders	0	0	1 (0.7) 1
Rash	0	0	1 (0.7) 1

System Organ Class Preferred Term	Sebetralstat 300 mg (N=86) n (%) m	Sebetralstat 600 mg (N=151) n (%) m	Placebo (N=138) n (%) m
Vascular disorders	0	1 (0.7) 1	0
Hot flush	0	1 (0.7) 1	0

n = number of patients experiencing the event; m = number of events

Notes: The Phase 2 and 3 Double-blind Safety Population included all randomized and treated patients from Phase 2 and 3 trials KVD900-201 and KVD900-301, respectively, during the double-blind treatment period

MedDRA Dictionary (Version 26.0) was used for coding AEs

System Organ Class terms are sorted using alphabetical order and preferred terms are sorted in decreasing frequency based on the total number of events on 'sebetralstat 300 mg'

Phase 1

In the Phase 1 Non-DDI Safety Population, headache was the only TEAE reported for $\geq 5\%$ of subjects in any treatment group that was considered by the investigator to be related to the IMP (1 subject [2.3%] who received <300 mg, 7 subjects [5.5%] who received 600 mg or equivalent, 8 subjects [9.5%] who received >600 mg, and 2 subjects [2.7%] who received placebo) (ISS Table 8.1); most of these events of headache occurred on-treatment.

Comments

The majority of TEAEs in the Phase 2-3 trials were assessed by investigators as not related to sebetralstat. The incidence of IMP-related TEAEs was similar across the treatment arms, with 2.3% of patients in the 300 mg group, 4.0% in the 600 mg group, and 4.3% in the placebo group reporting such events. Headache was the only IMP-related TEAE reported in more than one patient per treatment group, occurring in 1.3% of patients in the 600 mg sebetralstat group and 1.4% in the placebo group.

Adverse reactions (defined as IMP-related, on-treatment TEAEs occurring in $\geq 1\%$ of patients and at a higher rate than placebo) included dyspepsia and fatigue, each affecting one patient in the sebetralstat 600mg group.

In the Phase 1 Non-DDI studies, headache was the only IMP-related TEAE observed in $\geq 5\%$ of subjects in any treatment group. Its frequency increased with higher doses of sebetralstat, occurring in 5.5% of the 600 mg group and 9.5% of subjects receiving doses >600 mg. These findings suggest a dose-dependent relationship for headache but remain within acceptable safety margins.

Study KVD900-301

Treatment-related TEAEs were reported for 2 (2.3%) patients (2 events) in the 300 mg KVD900 group, 3 (3.2%) patients (4 events) in the 600 mg KVD900 group, and 4 (4.8%) patients (5 events) in the placebo group.

The most common treatment-related TEAEs (i.e., TEAEs that occurred in more than 1% of patients [2 or more regardless of treatment group]) were nausea (1 treatment-related TEAE each was reported for 1 [1.1%] patient in the 600 mg KVD900 group and 1 [1.2%] patient in the placebo group), dyspepsia (1 treatment-related TEAE each was reported for 1 [1.2%] patient in the 300 mg KVD900 group and 1 [1.1%] patient in the 600 mg KVD900 group), and headache (1 treatment-related TEAE each was reported for 1 [1.1%] patient in the 600 mg KVD900 group and 1 [1.2%] patient in the placebo group).

Table 19. Treatment-Emergent Adverse Events Related to the IMP by System Organ and preferred term (Safety net)

	300 mg KVD900 (N=86)	600 mg KVD900 (N=93)	Placebo (N=83)
System Organ Class	n (%)	n (%)	n (%)
Preferred Term	n (%) E	n (%) E	n (%) E
Total number of TEAEs	2 (2.3) 2	3 (3.2) 4	4 (4.8) 5
Gastrointestinal disorders	1 (1.2) 1	2 (2.2) 2	1 (1.2) 1
Dyspepsia	1 (1.2) 1	1 (1.1) 1	0
Nausea	0	1 (1.1) 1	1 (1.2) 1
General disorders and administration	1 (1.2) 1	0	0
Fatigue	1 (1.2) 1	0	0
Nervous system disorders	0	1 (1.1) 1	2 (2.4) 2
Headache	0	1 (1.1) 1	1 (1.2) 1
Dysgeusia	0	0	1 (1.2) 1
Reproductive system and breast disorders	0	0	1 (1.2) 1
Menstruation irregular	0	0	1 (1.2) 1
Skin and subcutaneous tissue disorders	0	0	1 (1.2) 1
Rash	0	0	1 (1.2) 1
Vascular disorders	0	1 (1.1) 1	0
Hot flush	0	1 (1.1) 1	0

Notes: At each level of patient summarization, a patient was counted once if the patient reported 1 or more events.

n represents the number of patients at each level of summarization. N is number of patients randomized using a permuted-block randomization method to ensure a balanced assignment to each of the 6 treatment sequences, to receive that received 300 mg KVD900, 600 mg KVD900, or matching placebo for the analyzed IMP-treated HAE attacks, according to the actual treatment received. [E] represents the number of events at each level of summarization.

Adverse events were coded using MedDRA Version 26.0.

On-treatment

Overall, 2 on-treatment, treatment-related TEAEs were reported for 2 [2.3%] patients in the 300 mg KVD900 group, 2 on-treatment, treatment-related TEAEs were reported for 2 [2.2%] patients in the 600 mg KVD900 group, and 5 on-treatment, treatment-related TEAEs were

reported for 4 [4.8%] patients in the placebo group) were reported to be of mild or moderate severity. The most common on-treatment, treatment related TEAEs (i.e., TEAEs that occurred in more than 1% of patients [2 or more regardless of treatment group]) reported by preferred term were headache (1 on-treatment, treatment-related TEAE each was reported for 1 [1.1%] patient in the 600 mg KVD900 group and 1 [1.2%] patient in the placebo group) and nausea (1 on-treatment, treatment-related TEAE each was reported for 1 [1.1%] patient in the 600 mg KVD900 group and 1 [1.2%] patient in the placebo group).

Study KVD900-201

Overall, 7/68 subjects (10.3%) experienced at least 1 drug-related TEAE.

Overall, the majority of study drug-related TEAEs were experienced by only 1 subject each, with the exception of headache (4 events experienced by 2 subjects [2.9%]) and flushing (2 events experienced by 2 subjects [2.9%]).

There was no clear pattern or discernible trends in study drug-related TEAEs following treatment with KVD900 or placebo.

Table 20. Summary of Study Drug-related Treatment-Emergent Adverse Events (Safety Set)

System Organ Class Preferred Term	Number of Event/Subjects (%)				
	Part 1	Part 2		KVD900 Combined (N=68)	Overall (N=68)
	600 mg KVD900 (N=68)	600 mg KVD900 (N=58)	(Placebo) (N=55)		
Any Study Drug-Related TEAEs	8 / 5 (7.4%)	3 / 3 (5.2%)	2 / 2 (3.6%)	11 / 6 (8.8%)	13 / 7 (10.3%)
Gastrointestinal disorders	1 / 1 (1.5%)	1 / 1 (1.7%)	1 / 1 (1.8%)	2 / 2 (2.9%)	3 / 3 (4.4%)
Abdominal pain upper	-	1 / 1 (1.7%)	-	1 / 1 (1.5%)	1 / 1 (1.5%)
Anal incontinence	-	-	1 / 1 (1.8%)	-	1 / 1 (1.5%)
Nausea	1 / 1 (1.5%)	-	-	1 / 1 (1.5%)	1 / 1 (1.5%)
General disorders and administration site conditions	1 / 1 (1.5%)	-	-	1 / 1 (1.5%)	1 / 1 (1.5%)
Malaise	1 / 1 (1.5%)	-	-	1 / 1 (1.5%)	1 / 1 (1.5%)
Musculoskeletal and connective tissue disorders	1 / 1 (1.5%)	1 / 1 (1.7%)	-	2 / 1 (1.5%)	2 / 1 (1.5%)
Back pain	1 / 1 (1.5%)	1 / 1 (1.7%)	-	2 / 1 (1.5%)	2 / 1 (1.5%)
Nervous system disorders	3 / 3 (4.4%)	1 / 1 (1.7%)	1 / 1 (1.8%)	4 / 3 (4.4%)	5 / 3 (4.4%)
Dizziness	1 / 1 (1.5%)	-	-	1 / 1 (1.5%)	1 / 1 (1.5%)
Headache	2 / 2 (2.9%)	1 / 1 (1.7%)	1 / 1 (1.8%)	3 / 2 (2.9%)	4 / 2 (2.9%)
Vascular disorders	2 / 2 (2.9%)	-	-	2 / 2 (2.9%)	2 / 2 (2.9%)
Flushing	2 / 2 (2.9%)	-	-	2 / 2 (2.9%)	2 / 2 (2.9%)

Abbreviations: TEAE=treatment-emergent adverse event

The denominator for each percentage is the number of subjects in the Safety Set within a treatment category.

A subject is counted only once per SOC and PT within a treatment category.

Study drug-related defined as relationship classified as "Suspected".

Study KVD900-302

Overall, 8 (9.5%) patients reported 18 TEAEs related to the IMP. The IMP-related TEAEs included influenza-like illness (Grade 2), arthralgia (Grade 2), headache (Grade 1 and Grade 2), skin burning sensation (Grade 2), vomiting (Grade 2), tremor (Grade 1), diarrhoea (Grade 3), nausea (Grade 2), and urticaria (Grade 1).

All IMP-related TEAEs were reported within 3 days of IMP administration (on-treatment), except for the TEAEs of Grade 2 arthralgia, Grade 2 vomiting, and Grade 3 diarrhoea.

Table 22. Treatment-Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Rollover (N=50) n (%) E	Non-Rollover (N=34) n (%) E	Total (N=84) n (%) E
All related treatment-emergent adverse events	4 (8.0) 8	4 (11.8) 10	8 (9.5) 18
Gastrointestinal disorders	0	2 (5.9) 7	2 (2.4) 7
Diarrhea	0	1 (2.9) 5	1 (1.2) 5
Nausea	0	1 (2.9) 1	1 (1.2) 1
Vomiting	0	1 (2.9) 1	1 (1.2) 1
General disorders and administration site conditions	1 (2.0) 2	0	1 (1.2) 2
Influenza-like illness	1 (2.0) 2	0	1 (1.2) 2
Musculoskeletal and connective tissue disorders	1 (2.0) 1	0	1 (1.2) 1
Arthralgia	1 (2.0) 1	0	1 (1.2) 1
Nervous system disorders	2 (4.0) 3	2 (5.9) 2	4 (4.8) 5
Headache	2 (4.0) 3	1 (2.9) 1	3 (3.6) 4
Tremor	0	1 (2.9) 1	1 (1.2) 1
Skin and subcutaneous tissue disorders	1 (2.0) 2	1 (2.9) 1	2 (2.4) 3
Skin burning sensation	1 (2.0) 2	0	1 (1.2) 2
Urticaria	0	1 (2.9) 1	1 (1.2) 1

Note: At each level of patient summarization, a patient is counted once if the patient reported one or more events.

N represents the number of patients at each level of summarization.

E represents the number of adverse events at each level of summarization.

Adverse events were coded using MedDRA, Version 26.0.

On-treatment drug-related TEAEs

Overall, 7 (8.3%) patients reported 15 TEAEs related to the IMP.

Comment

Overall, the number of TEAE was low amongst all treatment groups, with lower levels of TEAEs in the Sebtralstat 300mg group compared to Placebo.

The most common treatment-related TEAEs attributable to Sebtralstat was headaches, nausea and dyspepsia. This was also seen when classified by on-demand treatment TEAEs (those with TEAEs within 3 days of the taking the IMP).

There was one case of a severe grade 4 TEAE in the Sebtralstat 300mg group, however this was a intervertebral disc protrusion and was not considered related to the drug.

Clinical Laboratory findings, Vital Signs and ECGs

Across all trials, there were no trends in clinical laboratory evaluations, including liver function tests, associated with sebetralstat. No safety signals were observed in clinical

laboratory results. No patients in Phase 2-3 trials reported TEAEs associated with clinical laboratory evaluations that were considered related to the IMP.

No clinically significant differences were observed between sebetralstat versus placebo in any post-baseline vital sign value or 12-lead ECG result.

The results from the cardiodynamic evaluation in KVD900-109 demonstrated that sebetralstat has no clinically relevant effect on heart rate or on cardiac conduction (i.e. the PR and QRS intervals). Based on the concentration-QTc analysis, an effect on $\Delta\Delta QTc F$ exceeding 10 ms can be excluded up to sebetralstat plasma concentrations of ~16,900 ng/mL. Note: a mean C_{max} of 16,900 ng/mL is greater than that predicted to be achieved in all recommended dosing scenarios and is greater than the C_{max} predicted to arise if 2 administrations of 300 mg were to be taken at once with a strong CYP3A4 inhibitor.

Safety in special populations

Sub-population analyses were performed to evaluate drug-demographic interactions. Overall, the safety profile of sebetralstat was similar across all subgroups analyzed, including age, race, and geographic region.

Pregnancy and Lactation

There are no clinical data to date from the use of sebetralstat in pregnant or lactating women. In non-clinical studies, there was limited placental transfer when sebetralstat was administered to rats. Studies in pregnant rats and rabbits indicate that sebetralstat administration did not cause embryofetal harm at clinically relevant exposures. Data in the rat have shown excretion of sebetralstat and/or its metabolites in milk without adverse effects in suckling rats. No effect on fertility was observed in animal studies.

Pediatric Use

KalVista agreed to an initial pediatric investigation plan (PIP) with the EMA on 4 September 2020 (P/0416/2020). Two further PIP modifications were agreed prior to MAA submission (P/0379/2022 and P/0476/2023).

Twenty-one pediatric patients ≥ 12 to < 18 years (3.1% of the All-Subjects Safety Population) of age were treated with sebetralstat in Phase 3 trials. No differences in safety findings were observed between pediatric and adult populations.

Overall in the Phase 2-3 Double-blind Safety Population (representing KVD900-301 trial data), TEAEs were reported for a single pediatric patient in each treatment group (1 patient [10.0%] who received 300 mg [1 mild event of blood urine present]; 1 patient [9.1%] who received 600 mg [1 moderate event of vomiting]; and 1 patient [11.1%] who received placebo [1 mild event of influenza]). The risk differences between 300 mg or 600 mg versus placebo were -1.1% (-28.8, 26.6) and -2.0% (-28.7, 24.6), respectively. The events of vomiting and influenza occurred while on-treatment. None of the events reported in pediatrics were considered related to the IMP, none were SAEs, and none led to trial discontinuation. The safety and efficacy of sebetralstat in pediatrics under 12 years has not yet been established. No data are available.

Adolescents

The pathogenesis of HAE is well-established and understood and that there would not be expected differences between adolescents and adults. Therefore, the effect of Sebetralstat in inhibiting plasma kallikrein would be the same between these population groups.

In terms of safety, no adverse event was noted to be related to Sebetralstat use.

Geriatric Use

Ten geriatric patients (aged ≥ 65 years) (1.5% of the All-Subjects Safety Population) participated in clinical trials, including 6 patients (2.3%) in Phase 2-3 trials (of whom 5 received sebetralstat) and 4 subjects (0.9%) in Phase 1 trials.

None of the TEAEs reported in geriatric adults were considered related to the IMP, none were SAEs, and none led to trial discontinuation.

Renal Impairment

Patients who had estimated glomerular filtration rate (eGFR) ≤ 90 mL/min/1.73m² were not excluded from participating in trials; 19.5% of patients in the All-Subjects Safety Population enrolled had an eGFR less than or equal to that rate. There have been no clinical renal safety findings considered related to the IMP in healthy subjects or patients with HAE, including reduced eGFR.

Hepatic Impairment

Hepatic function classification is based on Child-Pugh score:

- Mild hepatic impairment: Child-Pugh Grade A (score 5 to 6 points)
- Moderate hepatic impairment: Child-Pugh Grade B (score 7 to 9 points)
- Severe hepatic impairment: Child-Pugh Grade C (score 10 to 15 points)

In KVD900-104, a single oral administration of 600 mg sebetralstat was well tolerated by subjects with mild or moderate hepatic impairment and subjects with normal hepatic function. No TEAEs were reported in this trial.

There were no remarkable findings in ECG results including no QTc prolongation. Changes in vital signs and clinical laboratory assessments were unremarkable.

Based on the PK and safety profile of sebetralstat, including after supratherapeutic doses in KVD900-109 (the TQT trial), no dose adjustment is required for patients with mild or moderate hepatic impairment. Use of sebetralstat in patients with severe hepatic impairment is not recommended.

Overdose

No TEAEs of overdose have been reported.

Dose levels up to 3,000 mg over a 2-hour period have been administered in the clinical development program (KVD900-109). No trends or changes to the safety profile were observed with this supratherapeutic dose level. No SAEs or severe TEAEs were reported, and there were no TEAEs leading to trial discontinuation. The TEAEs reported were consistent with the type, incidence, and severity of events reported in other Phase 1 trials.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

Two Phase 1 DDI clinical trials have been completed (KVD900-106 and KVD900-112), which evaluated the impact of strong, moderate and weak CYP3A4 inhibitors and inducers on the PK of sebetralstat. Safety data from these two trials were integrated in the Phase 1 DDI Safety Population. In all treatment groups in both DDI trials, sebetralstat administered alone and with co-administrators was well tolerated by the healthy subjects in these trials.

There were no notable differences in the safety profile for subjects in the DDI trials compared with the Phase 1 non-DDI trials.

Discontinuation due to AEs

Across the clinical development program, 6 patients or subjects in sebetralstat treatment groups reported TEAEs leading to trial discontinuation (4 patients in KVD900-302) or withdrawal of the IMP (2 healthy subjects in Phase 1 DDI trials).

One of the TEAEs leading to trial discontinuation in KVD900-302 was also an SAE (intracranial mass, considered not related to IMP). Two TEAEs leading to trial discontinuation in KVD900-302 occurred on-treatment (i.e. within 3 days after IMP administration) and were considered by the investigator to be related to the IMP (events of skin burning sensation and nausea); both of these events resolved without intervention. The remaining TEAE leading to trial discontinuation in KVD900-302 was an event of ALT increased that occurred subsequent to an SAE of viral meningitis; the event was considered not related to IMP.

One of the TEAEs leading to trial discontinuation in KVD900-302 was also an SAE (intracranial mass, considered not related to IMP). Two TEAEs leading to trial discontinuation in KVD900-302 occurred on-treatment (i.e. within 3 days after IMP administration) and were considered by the investigator to be related to the IMP (events of skin burning sensation and nausea); both of these events resolved without intervention. The remaining TEAE leading to trial discontinuation in KVD900-302 was an event of ALT increased that occurred subsequent to an SAE of viral meningitis; the event was considered not related to IMP.

Table 23. Treatment-emergent AEs Leading to Trial Discontinuation or Withdrawal of the IMP, Patients in Any Sebetralstat Treatment Group

Trial	System Organ Class/ Preferred Term	Treatment	Severity/ Causality	Outcome	SAE	On- Treatment
KVD900-302	Investigations/ ALT increased	600 mg	Moderate/ Not related	Not recovered/ Not resolved	No	No
KVD900-302	Nervous system disorders/ Intracranial mass	600 mg	Moderate/ Not related	Not recovered/ Not resolved	Yes	No
KVD900-302	Skin and subcutaneous tissue disorders/ Skin burning sensation	600 mg	Moderate/ Related	Recovered/ Resolved	No	Yes
KVD900-302	Gastrointestinal disorders/ Nausea	600 mg	Moderate/ Related	Recovered/ Resolved	No	Yes
KVD900-106	Investigations/ AST increased	600 mg alone	Mild/ Related	Recovered/ Resolved	No	Yes
KVD900-112	Infections and infestations/ COVID-19	600 mg alone	Mild/ Not related	Recovered/ Resolved	No	Yes

A total of 213 patients with HAE Type I or II have received the IMP (sebetralstat or placebo) in Phase 2-3 trials to date. Participation is ongoing for 90 patients (42.3%) (all in KVD900-302). Seventy-four (34.7%) patients completed the respective trials to date (i.e. treated all attacks in KVD900-201 or KVD900-301, completed the trial completion visit, and did not rollover to KVD900-302).

Discontinuations were classified as due to AE, protocol violation, lost to follow-up, physician decision, withdrawal by participant, or trial termination by sponsor. As the double-blind Phase 2-3 trials were event-driven trials, they were designed to end once a pre-specified number of evaluable attacks were treated with IMP in each trial. At that point, all ongoing patients' participation in the trial was terminated and a final trial visit was performed. Patients whose participation was terminated when the trial ended were allowed to enroll in KVD900-302. Accordingly, 30 patients (14.1%) discontinued for this reason (coded as trial termination by Sponsor in electronic data capture). Additional reasons for discontinuation in Phase 2-3 trials were withdrawal by participant (8 patients [3.8%]), AE, lost to follow-up, and other (3 patients [1.4%] each), and protocol violation and physician decision (1 patient [0.5%] each).

Of the 457 subjects who received IMP in Phase 1 trials, 452 (98.9%) completed the respective trials. Five subjects (1.1%) discontinued from the trial early; reasons for withdrawal reported by more than a single subject was AE and lost to follow-up (2 subjects [0.4%] each).

Table 24. All-Subjects Safety Population: Summary of Disposition

	Phase 1 Trials (N=457)	Phase 2 and 3 Trials (N=213)	Overall (N=670)
Enrolled, n	457	213	670
Completed Trial, n (%)	452 (98.9)	74 ^a (34.7)	526 (78.5)
Participation is Ongoing ^b , n (%)	-	90 (42.3) ^c	90 (13.4)
Discontinued Trial ^d , n (%)	5 (1.1)	49 (23.0)	54 (8.1)
Adverse Event	2 (0.4)	3 (1.4)	5 (0.7)
Protocol Violation	0	1 (0.5)	1 (0.1)
Lost to Follow-up	2 (0.4)	3 (1.4)	5 (0.7)
Physician Decision	0	1 (0.5)	1 (0.1)
Withdrawal by Participant	1 (0.2)	8 (3.8)	9 (1.3)
Trial Termination by Sponsor	0	30 (14.1)	30 (4.5)
Other	0	3 (1.4)	3 (0.4)

Notes: The All-Subjects Safety Population includes all treated subjects in Phase 1-3 trials

Phase 1 trials include: KVD900-101, KVD900-102, KVD900-103, KVD900-104, KVD900-106, KVD900-107, KVD900-108, KVD900-109, KVD900-110, and KVD900-112

Phase 2 and 3 trials include: KVD900-201, KVD900-301, and KVD900-302

^a Trial completers included patients from KVD900-201 and KVD900-301 who treated all attacks, completed the trial completion visit, and did not rollover to KVD900-302

^b Ongoing patients are from KVD900-302. KVD900-301 was terminated by sponsor due to the observation of a sufficient number of attacks

^c As a function of the rollover design, a subset of patients considered "ongoing" may have received the IMP in KVD900-301 and were enrolled in KVD900-302 but have not yet treated any attacks in KVD900-302. Therefore, pooled numbers may vary from individual CSRs

^d The percentage for each reason for discontinuation was based on total number of subjects enrolled

Comment

Across Phase 2-3 trials, six patients discontinued due to TEAEs, with four cases occurring in KVD900-302. Among these, two events (skin burning sensation and nausea) were on-treatment and assessed as related to the IMP. Both events resolved without intervention, suggesting a transient and manageable impact. One discontinuation was due to an SAE (intracranial mass), which was deemed unrelated to the IMP.

In Phase 1 trials, five subjects (1.1%) discontinued early, with two cases attributed to TEAEs. Both events resolved without sequelae. This low discontinuation rate further emphasises the tolerability of sebetralstat in healthy subjects.

The low rate of discontinuation due to TEAEs across the development program, combined with the resolution of IMP-related events, highlights the acceptable tolerability of sebetralstat. The data do not raise significant concerns regarding drug safety or its potential to limit patient adherence in future clinical or real-world settings.

Post marketing experience

Ekterly is currently being used in the Early Access to Medicines Scheme (EAMS).

Summary and Conclusions on clinical safety

The clinical development programme for sebetralstat has involved a total of 670 participants, encompassing both healthy individuals and patients with hereditary angioedema (HAE), across various trial phases. Among these, 213 participants were HAE patients enrolled in Phase 2 and Phase 3 studies, while 457 were healthy subjects in Phase 1 trials. Of the patient population, 208 individuals received at least one administration of sebetralstat, with 198 patients treating

a cumulative total of 879 HAE attacks. This dataset includes 21 paediatric patients (aged 12–18 years) who treated 159 attacks and five geriatric patients (aged ≥ 65 years) who treated 27 attacks, ensuring representation across the intended commercial age groups.

Data from the pivotal Phase 3 trials show that the majority of HAE attacks were effectively managed with a single dose of sebetralstat. Specifically, 66.3% of attacks were resolved with a 300 mg dose, 77.1% with a 600 mg dose, and 71.7% with placebo. For cases requiring additional dosing, the need remained consistent over time, with 92.7% of multi-dose cases resolved with exactly two doses. Long-term data from the ongoing open-label KVD900-302 trial further demonstrate the effectiveness of sebetralstat, as only 11.9% of patients required three administrations, representing 2.8% of all treated attacks.

In terms of long-term exposure, data from KVD900-302 indicate that the treatment burden of sebetralstat is manageable. The median dosing frequency was 2.2 administrations per month. One patient treated 37 attacks over the trial duration, requiring a maximum of 56 administrations. Notably, 53.6% of participants had trial exposure for at least three months, 26.2% for six months, and 3.6% for a year, providing sufficient data to assess safety over time. Paediatric and geriatric subgroups were included, with results confirming the applicability of sebetralstat for these populations. Paediatric patients treated 159 attacks, while geriatric patients treated 27 attacks, showing consistent efficacy and tolerability.

Safety data across all clinical phases consistently demonstrate that sebetralstat is well-tolerated. Treatment-emergent adverse events (TEAEs) were predominantly mild or moderate in severity, with no evidence of dose-related increases in frequency or severity. Headache was the most commonly reported TEAE, occurring at rates comparable to placebo, and did not indicate a significant safety concern. TEAEs deemed related to the investigational medicinal product (IMP) were infrequent, with 2.3% in the 300 mg group, 4.0% in the 600 mg group, and 4.3% in the placebo group. Only one severe TEAE (Grade 3 intervertebral disc protrusion) was reported in the 300 mg group, which was unrelated to sebetralstat.

No significant safety signals, such as severe adverse events (SAEs), were identified. Among the eight SAEs reported in six patients, none occurred within three days of IMP administration or were considered related to sebetralstat. Importantly, no deaths were reported throughout the clinical programme. The low discontinuation rate due to TEAEs further underscores the favourable tolerability profile of sebetralstat. In Phase 2-3 trials, six patients discontinued due to TEAEs, two of which (skin burning sensation and nausea) were related to the IMP but resolved without intervention. Although discontinuations were infrequent, the reported cases of skin burning sensation and nausea related to the IMP in KVD900-302 highlight the potential for adverse reactions that may impact patient adherence.

Sub-population analyses confirmed a consistent safety profile across demographic groups, including age, race, and geographic region. In paediatric patients aged 12–18 years, TEAEs were reported in one patient per treatment group (300 mg, 600 mg, and placebo), with none deemed related to the IMP. Similarly, among geriatric patients aged ≥ 65 years, TEAEs were infrequent and unrelated to sebetralstat. Pregnancy and lactation data remain limited, with no clinical reports available to date. However, non-clinical studies in pregnant animals revealed no embryofetal harm or adverse effects in suckling offspring.

Pharmacokinetic assessments indicate that renal excretion is not the primary route of sebetralstat elimination, with less than 9% of the dose excreted unchanged in urine. As a result, a dedicated renal impairment trial was deemed unnecessary. No clinically significant differences were observed in vital signs, ECG parameters, or clinical laboratory data between

sebetralstat and placebo, further supporting the absence of systemic toxicity or significant metabolic effects.

Overall, the clinical development programme for sebetralstat demonstrates its safety and efficacy in treating HAE attacks across diverse populations. The drug's well-tolerated safety profile, combined with its effectiveness in resolving attacks with minimal dosing, supports its potential for broad clinical application.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of These products in the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N

Annex 1

Summary of fulfilment of the criteria for orphan drug designation

Product: *Ekterly 300 mg film-coated tablets.*
Active substance: *sebetralstat*
Orphan Designation Number: *PL 46326/0001/OD1*

Background:

This application was evaluated for fulfilment of orphan designation criteria and the designation criteria were considered fulfilled.

Orphan condition

The orphan condition is Hereditary Angioedema. This is acceptable and in line with the guidance on what constitutes a valid condition. Hereditary angioedema falls under a specific category of angioedema without wheals. HAE is an autosomal dominant genetic disorder caused by one of more than 450 different mutations in the serine protease inhibitor G1 (SERPING1) gene which leads to either a deficiency in the serine protease inhibitor, C1 inhibitor (C1INH); classified as Type I HAE, or a dysfunction of C1INH; classified as Type II HAE. A third, very rare type of HAE with normal C1INH (HAE nC1INH), has also been documented.

Orphan indication

The orphan indication the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.

Life threatening/ debilitating condition

The condition is life-threatening or seriously debilitating. HAE is a life-long chronic condition where patients experience sporadic attacks of angioedema that can be psychologically and socially distressing to experience and therefore impact quality of life. The condition can occur at all anatomic sites and laryngeal involvement can be fatal if not timeously managed.

Prevalence of the Condition in Great Britain (GB)

Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects less than 5 in 10,000 people in GB; the point prevalence is estimated to be in the range of 0.17 to 0.46 in 10,000. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of diagnosis/prevention/ treatment

The following methods have been identified:

There are two types of treatment for HAE:

- on-demand treatments to treat HAE attacks
- prophylactic treatments which are taken to prevent attacks

It is important to note that patients taking prophylactic treatment continue to have “breakthrough” attacks including those affecting the larynx and are therefore advised by current HAE treatment guidelines to always carry on-demand treatment with them (Maurer, 2022; Busse, 2021). Sebetralstat is being developed for the on-demand treatment of HAE attacks. The

currently available on-demand treatments for HAE are listed in Table 2. The current prophylactic treatments for HAE are listed in Table 3.

Table 11. Current on-demand treatments for HAE

Name	Type of product	Route	Indication (HAE specific)
Berinert	Plasma derived C1INH	iv	Hereditary angioedema Type I and II (HAE). Treatment and pre-procedure prevention of acute episodes
Firazyr (icatibant)	Bradykinin B2 Antagonist	sc	Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1 esterase-inhibitor deficiency
Ruconest	Recombinant derived C1INH	iv	For treatment of acute angioedema attacks in adults, adolescents and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency
Cinryze	Plasma derived C1INH	iv	Treatment of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE). (Also indicated for prophylactic treatment – see Table 3)

Name	Type of product	Route	Indication (HAE specific)
Cinryze	Plasma derived C1INH	iv	Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment
Takhzyro (lanadelumab)	Plasma kallikrein inhibitor	sc	For routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older
Orladeyo (berotralstat)	Plasma kallikrein inhibitor	oral	Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older

As noted in Table 3, there is another oral treatment for HAE, Orladeyo (berotralstat). However, Orladeyo is indicated for “routine prevention of recurrent attacks” (i.e. prophylaxis). This is totally different to the indication that sebetralstat has been developed for which is for the on-demand treatment of HAE attacks.

As noted above, patients on prophylactic treatment continue to have “breakthrough attacks” and are advised by current HAE treatment guidelines to always carry an on-demand treatment with them.

Justification of significant benefit

Methods for the prevention or treatment of the orphan condition already exist in GB. Suitable justification has been provided that Ekterly 300 mg film-coated tablets provides a significant benefit to those affected by the condition as specified in the orphan indication.

Conclusion on acceptability of orphan designation

The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 15 July 2025