24 July 2025
EMA/266036/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ekterly

International non-proprietary name: sebetralstat

Procedure No. EMEA/H/C/006211/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AS	Active Substance
AST	AST aspartate aminotransferase
AUC	area under the concentration versus time curve
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BK	bradykinin
BMI	body mass index
BP	British Pharmacopoeia
BR2	bradykinin receptor 2
C1-INH	complement component 1 inhibitor
CI	confidence interval
CQA	Critical quality attribute
C_{max}	maximum observed concentration
CTR	clinical trial report
CV	coefficient of variation
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DDI	drug-drug interaction
DXS	dextran sulfate
ECG	electrocardiogram
eDiary	electronic diary
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
GA-NRS	General Anxiety Numeric Rating Scale
GCP	good clinical practice
GGT	gamma glutamyl transferase

HAE	hereditary angioedema
HK	high molecular weight kininogen
IcEV	intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
INR	international normalised ratio
IQR	interquartile range
IV	intravenous(ly)
LS	least-squares
nC1-INH	normal complement component 1 inhibitor
NE	not estimable
ODT	orally disintegrating tablet or orodispersible tablet
PBPK	physiologically based pharmacokinetic(s)
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
pH	potential hydrogen
PI	product information
PIP	paediatric investigation plan
PKa	plasma kallikrein
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PR	pulse rate
PRO	patient-reported outcome
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
TQT	thorough QT
VAS	Visual Analog Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Kalvista Pharmaceuticals (Ireland) Limited submitted on 25 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Ekterly, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2022.

Ekterly, was designated as an orphan medicinal product EU/3/22/2625 on 21 June 2022 in the following condition: treatment of hereditary angioedema.

The applicant applied for the following indication *'Ekterly is indicated for the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older'*.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0476/2023 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP EMEA-002723-PIP01-19-M02 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ekterly as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/ekterly

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active substance status

The applicant requested the active substance sebetralstat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13 October 2022	EMA/SA/0000098461	*Rosalía Ruano Camps and Ewa Balkowiec Iskra*

The protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

- Definition of the starting materials for the manufacturing of the active substance; proposed drug product specifications and commercial shelf-life determination.

- Adequacy of proposed package of nonclinical toxicology and safety pharmacology studies to support marketing authorisation, including submission of the final study report for the 2-year rat carcinogenicity study during the assessment.

- Design of the phase 3 trial KVD900-301 and open-label extension, in particular the choice of patient population, dose selection, choice of endpoints, statistical aspects; proposed safety database to support marketing authorisation; clinical pharmacology development programme, in particular with regards to renal impairment, hepatic impairment and drug-drug interactions studies.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	25 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 November 2024

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 March 2025
The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
– A GCP inspection at the sponsor site in the United Kingdom, two clinical investigator sites in Greece and in Portugal 16/12/2024 and 10/02/2025. The outcome of the inspection carried out was issued on	21 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 May 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 May 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ekterly on	24 July 2025
The CHMP adopted a report on similarity of Ekterly with Takhzyro on	24 July 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hereditary angioedema (HAE) is a rare, chronic, genetic, debilitating, and potentially life-threatening disorder characterised by recurrent and often unpredictable attacks of BK-mediated swelling in many parts of the body, without the presence of hives.

Angioedema attacks are episodic with considerable variations in frequency and severity. Swelling has been shown to affect subcutaneous tissue (face, upper or lower extremities, genitals) in 82% of patients, abdominal organs (stomach, intestines) in 78% of patients, and the upper airway (larynx, tongue) in 27% of patients (Nordenfelt et al 2016). Laryngeal attacks are infrequent (<5% of attacks) but are potentially life-threatening. Approximately 50% of all patients with HAE experience at least one laryngeal attack during their lifetime.

Characteristics of HAE attacks are heterogenous among patients as well as across attacks within an individual patient (e.g. severity, location).

2.1.2. Epidemiology and risk factors, screening tools/prevention

The currently accepted prevalence of hereditary angioedema due to C1-inhibitor deficiency (C1-INH) is around 1 per 50,000 population corresponding to for Europe of 8984 patients. It is considered as a rare disease.

The first onset of HAE symptoms is variable, occurring in the first or second decade of life in most patients, with nearly half of patients experiencing symptoms by age 6 and approximately 90% of patients before age 20 (MacGinnitie 2014, Frank 2016).

On average, patients have HAE attacks every 1 to 3 weeks (Bernstein 2018). However, attack frequency is unpredictable and can vary greatly among patients and within individual patients.

2.1.3. Biologic features, aetiology and pathogenesis

HAE is caused by a deficiency in the C1-INH protein and characterised by unpredictable tissue swelling due to an increase in vascular permeability. Two forms of HAE due to C1-INH deficiency are described: HAE due to C1-INH quantitative deficiency (characterised by low antigenic and functional C1-INH levels) and HAE due to C1-INH dysfunction (characterised by normal or elevated antigenic but low functional C1-INH levels). These subtypes are traditionally referred to as type 1 and type 2, respectively and abbreviated as HAE-C1INH-Type1 and HAE-C1INH-Type2. HAE type 1 and type 2 account for approximately 90% and 10% of HAE cases respectively.

In rare cases, patients have a third type of HAE, nC1-INH-HAE (international nomenclature: HAE-nC1INH) (formerly referred to as HAE type III), in which antigenic and functional C1-INH levels are normal. This form is characterised by specific genetic mutations in the FXII, the plasminogen (PLG), the angiopoietin-1, the

kininogen 1, myoferlin, and heparan sulfate-glucosamine 3-O-sulfotrasnferase 6 gene, or due to an unknown cause and genetic background.

C1-INH inhibits key enzymes in the contact system, one of which is plasma kallikrein. Due to the deficiency in C1-INH associated with HAE, activated plasma kallikrein generates the vasoactive peptide hormone bradykinin, the mediator of vascular hyperpermeability that causes tissue swelling and pain.

2.1.4. Clinical presentation, diagnosis

HAE attacks often occur without an identified trigger; however, precipitating factors shown to contribute to the frequency of attacks include stress, trauma, infection, menstruation, and pregnancy, as well as various medications. If left untreated, attack symptoms will typically intensify over the first 12 to 36 hours, then gradually subside over 2 to 5 days. In patients with untreated or inadequately managed HAE attacks, the impact on quality of life is significant. Between attacks, patients may experience significant psychosocial burden due to the anxiety of when they may experience their next attack. Many patients with HAE modify their lifestyles to accommodate their disease, restricting their careers, partnerships, and recreational activities.

Information provided by the patients' association EURORDIS

A survey among 158 people living with HAE conducted in 2021 in France (by French centre of expertise of HEA) showed that stress, emotions and trauma were the leading factors associated with the onset of a crisis (quoted by 83%, 72% and 66% of respondents respectively). Other factors were infections (34%), dental care (32%), menstruation (27%), and surgery (25%), followed by hormonal therapy, pregnancy and other factors (note that stress can include fatigue, sleepless nights, insomnia).

One third of patients can experience erythema marginatum 24h before a crisis, but its occurrence is not a certainty of a crisis. C1 inhibitor levels are not a prognosis factor (of crisis, nor their severity).

When left untreated after early symptoms, the peak of the crisis can be reached in less than 1 hour for 6% of respondents, in 1 to 3 hours for 19%, in 3 to 6 hours by 21%, in 6 to 12 hours by 19%, more than 12 hours by 32%. When untreated, the crisis can last for 2 to 4 days (abdominal crisis, crisis of the face, of the limb extremities). When treated, it is usually controlled in less than 12 hours. When untreated, the crisis was reported as severe by 103/158 (65%), and moderate by 52/158 (33%) in average. When treated, 14/158 (9%) reported severe crisis unresponsive to treatment.

The psychological impact of the disease and the crisis was high for 34/158 respondents (21%) or moderate for 53/158 (34%) and light or absent for 71/158 (45%). 77/158 or (49%) reported a deleterious effect on daily life (school, work, social, family life).

2.1.5. Management

As illustrated in the table below, sebetralstat would be the first chemical competitive, reversible inhibitor of plasma kallikrein in the treatment of attacks, the other representative (small molecule) of this pharmacological class, berotralstat is only registered for prevention of recurrences. Moreover, this would be the first treatment of attacks for oral administration of particular convenience for patients, others being administered by parenteral route (IV, SC).

HAE attacks do not respond to antihistamines, corticosteroids or adrenaline. The treatments already available in Europe can be divided into the following categories, depending on whether they are for treatment of angioedema attacks, prophylactic treatment of angioedema attacks or pre-procedure prevention of angioedema attacks (before a medical, dental, or surgical procedure):

Treatment of acute attacks of HEA (on demand treatments)					
Date in year	Commercial denomination	INN	Method of administration	Population	Mechanism of action
2008	FIRAZYR 30 mg solution for injection in pre-filled syringe	icatibant	SC	Adults, adolescents and children aged 2 years and older	Selective competitive antagonist at the bradykinin type 2 (B2) receptor)
2010	RUCONEST 2100 Units powder for solution for injection.	conestat alfa Recombinant human C1 inhibitor	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2011	CINRYZE 500 IU powder and solvent for solution for injection	Plasma Human C1-esterase inhibitor.	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2013	BERINERT 500 IU powder and solvent for solution for injection/infusion	Plasma Human C1-esterase inhibitor.	IV or slowly infusion	Adults and children	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2025	***EKTERLY 300 mg film-coated tablet***	***sebetralstat***	***Oral use***	***Adult and adolescents aged 12 years and older***	***Inhibitor of plasma kallikrein***
Treatment for routine prevention of recurrent attacks of HAE (long term prophylaxis)					
2011	CINRYZE 500 IU powder and solvent for solution for injection	Plasma Human C1-esterase inhibitor.	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2018	TAKHZYRO 150 or 300 mg solution for injection in pre-filled syringe	lanadelumab	SC	Patients aged 2 years and older	Inhibitor of plasma kallikrein

2021	ORLADEYO 150 mg hard capsules	berotralstat	Oral use	Adult and adolescent patients aged 12 years and older	Inhibitor of plasma kallikrein
2025	ANDEMBRY 200 mg solution for injection	garadacimab	SC	Adult and adolescent patients aged 12 years and older	Inhibitor of plasma kallikrein
Pre-procedure prevention of angioedema attacks (before a medical, dental, or surgical procedure) (short term prophylaxis)					
2011	CINRYZE 500 IU powder and solvent for solution for injection	Plasma Human C1-esterase inhibitor.	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2013	BERINERT 500 IU powder and solvent for solution for injection/infusion	Human C1-esterase inhibitor.	IV or slowly infusion	Adults and children	Human C1-esterase inhibitor.

2.2. About the product

The drug product Ekterly is an immediate release film-coated tablet for oral use containing 300 mg of sebetralstat. New active substance status (NAS) is agreed for sebetralstat and sebetralstat is not considered similar to lanadelumab in accordance with Article 8(1) and (3) of Regulation (EC) No 141/2000.

The intended commercial presentation is a 300 mg immediate-release, yellow, oval, film-coated tablet.

Sebetralstat has been developed as an oral treatment for hereditary angioedema (HAE) attacks in adults and adolescents aged 12 years and older.

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.

Following oral administration, it is rapidly absorbed, resulting in near complete suppression of PKa activity as early as 15 minutes after dosing. Sebetralstat is intended to be taken by patients at the earliest recognition of an attack.

Ekterly is claimed for the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older.

2.3. Type of application and aspects on development

The applicant applied for a standard initial marketing authorisation. The clinical development program has included:

- Ten Phase 1 trials conducted in healthy subjects particularly pharmacokinetics studies (KVD900-101, KVD900-102, KVD900-103, KVD900-110)], drug-drug interaction studies (KVD900-106, KVD900-112), hepatic impairment study (KVD900-104) and thorough QT (TQT) study (KVD900-109).
- One Phase 2 double-blind, randomised, crossover, placebo-controlled, efficacy and safety trial in adult patients with HAE type 1 or 2 (KVD900-201). In part 2 of this study sebetralstat a 600 mg dose was administered (as film-coated tablets) as a single administration before or after placebo (separated by a 48h washout).
- One pivotal Phase 3, KONFIDENT study, double-blind, randomised, crossover, placebo-controlled multicentre trial, efficacy trial in adult and paediatric patients aged 12 years and older with HAE type 1 or 2 (KVD900 301). The scheme was up to two administrations of blinded tablet IMP administered at least 3 hours apart: sebetralstat 300 mg and 600 mg, or placebo
- One ongoing Phase 3, KONFIDENT-S study, open-label safety trial of long-term use of sebetralstat 600 mg in adult and paediatric patients aged 12 years and older with HAE type 1 or 2 that also provides supportive efficacy information (KVD900-302).

Of the thirteen studies presented in the dossier, only three tested the 300 mg dose: two phase I studies and the pivotal phase 3 study. Study KVD900-101 tested the 300 mg dose, as a powder in capsule formulation, study KVD900-110 and the pivotal study KVD900-301 tested the 300 mg dose, as white film-coated tablets. For commercial reasons, an oval tablet shape (rather than a round tablet) and the yellow colour were selected. The coating is non-functional and neither the colour nor the shape changes will impact the properties of the tablet (please see Quality AR for discussion on the different formulations used across studies).

The following interactions with the EMA have taken place during the development programme:

- Initial protocol assistance received (EMA/SA/0000098461) on 13 October 2022;
- Initial paediatric investigation plan (PIP) received on 4 September 2020 (P/0416/2020). Two further PIP amendments were agreed prior to MAA submission (P/0379/2022 and P/0476/2023).
- Orphan drug designation (EU/3/22/2625; 21 June 2022) granted for the treatment of hereditary angioedema.
- Confirmation of eligibility to submit via the centralised procedure (Union Marketing Authorisation under Article 3[1] – Indent 4 – Orphan designated medicinal product of Regulation [EC] No 726/2004) on 13 October 2022.
- Pre-submission advice received on 20 April 2024 (EMA/172843/2021) and a rapporteur meeting was held on 23 May 2024.

With regard to clinical aspects, the scientific advice covered the design of the phase 3 KVD900-301 study and the open-label extension study KVD900-302, in particular the choice of patient population, dose selection, choice of endpoints, statistical aspects; the proposed safety database to support the marketing authorisation;

the clinical pharmacology development programme, in particular with regard to renal impairment, hepatic impairment and drug-drug interaction studies.

The CHMP Guidelines were followed.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 300 mg of sebetralstat as active substance.

Other ingredients of the tablet core are: microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone K30 (E1201), and magnesium stearate (E470b). Ingredients of the film-coating are: macrogol poly(vinyl alcohol) grafted copolymer (E1209), talc (E553b), titanium dioxide (E171), glycerol monocaprylocaprate (Type 1) (E471), poly(vinyl alcohol) (E1203), iron oxide yellow (E172), iron oxide black (E172), maltodextrin (E1400), guar galactomannan (E412), hypromellose (E464), and triglycerides, medium-chain.

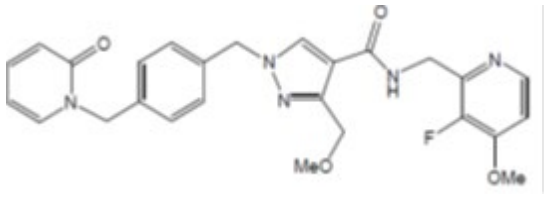
The product is available in oriented polyamide nylon/aluminium/polyvinyl chloride (oPA/Al/PVC) with aluminium lidding blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of sebetralstat is *N*-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide corresponding to the molecular formula $C_{26}H_{26}FN_5O_4$. It has a molecular weight of 491.52 g/mol and the following structure:

Figure 1. Active substance structure



The chemical structure of sebetralstat was elucidated by a combination of high resolution mass spectrometry (MS, accurate mass), ^{1}H NMR, ^{13}C NMR, elemental analysis, and infra-red spectroscopy. The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), gravimetric vapor solution (GVS) and X-ray powder diffraction (XRPD).

The active substance is a white to off-white crystalline powder, slightly hygroscopic and the hydration is reversible with no evidence of hysteresis. Sebetralstat is highly soluble in acidic media (33 mg/mL in 0.1 M HCl and 11 mg/mL in fasted state simulated gastric fluid (FaSSGF)). Solubility is low in higher pH media and simulated intestinal fluids. For the purposes of BCS classification it was determined that sebetralstat has low solubility. Whilst sebetralstat has moderate *in vitro* permeability (demonstrated by *in vitro* Caco-2 cell

assays) and is generally well absorbed after oral administration in humans, it is categorised as a BCS Class IV compound. This classification is based on low solubility in addition to no definitive demonstration of >85% oral absorption in humans.

Sebetralstat has a non-chiral molecular structure.

Polymorphism has been observed for sebetralstat. Two anhydrous/non-solvated forms of sebetralstat (form 1 and form 6) have been identified and fully characterised. Sebetralstat can also exist in several hydrated crystalline forms. Form 1 is the form chosen and used throughout development and intended for commercial manufacturing. All active substance batches used for clinical development activities were determined to be form 1 by XRPD. The validated active substance synthetic route consistently produces sebetralstat as form 1. The formation of form 6 during synthesis of sebetralstat is avoided by specific process conditions as form 6 has been formed only under very specific conditions. Although the two pure forms are readily distinguished by XRPD, small amounts of form 6 present in form 1 would not be visible by the XRPD test and so a DSC method is also employed to demonstrate conformance with form 1 in the active substance specification.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by a single manufacturer. Satisfactory GMP documentation (QP declaration) has been provided.

Sebetralstat is synthesised using a convergent synthesis from 3 starting materials via several isolated and non-isolated intermediates. Expected yields, process scheme and the narrative of the synthesis including quantities of materials, and in-process controls have been presented and are satisfactory.

To note, in October 2022, scientific advice on the acceptability of the starting materials was provided to the applicant (EMA/SA/0000098461) which has been followed. The specifications for raw materials in general include appearance, identity and purity/assay with adequate acceptance criteria. Additionally, specifications for seeding crystals of an intermediate and the active substance have been provided, and it has been confirmed that the seed material complies with the specifications for the respective intermediate and the active substance. The acceptable specification for potable water from the AS manufacturer has been provided.

Critical process parameters are listed, rationale for their designation as critical is given and their control strategy is presented. In addition, in-process controls (IPCs) are listed with their acceptance criteria. The description of analytical procedures used for in-process controls have been added. Adequate IPCs are applied during the synthesis.

During the proposed process, six intermediates are isolated.

The manufacturing process has been validated by an initial validation campaign on three commercial scale batches at each stage of the manufacturing process and thereafter by continuous process verification (CPV). In line with ICH Q11 only a brief summary of the process validation has been provided in the dossier as the active substance is a non-sterile chemical entity. A major objection (MO1) was raised regarding the process as more information (e.g. details on specific steps of the manufacturing process, starting material batch results) was requested to provide assurance that the process is well controlled and results in consistent batch-to-batch quality of the active substance. In response, the applicant presented a phase 1 validation report, providing the requested data and resolving the major objection.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities are listed with their structure, origin and purge information. Besides the control of impurities by the active substance specification, other points of control that were established during process development are defined, including limits set in the starting materials or intermediates specifications as well as IPCs.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in double low-density polyethylene (LDPE) bags placed in high density polyethylene (HDPE) drums, which provide protection against light. The primary packaging complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for appearance, identity (FTIR, HPLC), polymorphic form (XRPD, DSC), water content (KF), residue on ignition (Ph. Eur.), assay (HPLC), impurities (HPLC, GC), elemental impurities (ICP/MS), residual solvents (HS-GC), particle size (Ph. Eur.), and microbial limit (Ph. Eur.).

The active substance specification is comprehensive and appropriate.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on five commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from eight commercial scale batches of active substance from the proposed commercial manufacturer stored in the intended commercial package according to the ICH guidelines were provided.

The following parameters were tested: appearance, water content, related substances, assay, XRPD, microbiological purity. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Photostability testing was performed on three commercial scale batches. Sebetralstat should therefore be stored protected from light.

Results on stress conditions (high temperature, light, oxidation and acid and base hydrolysis) were also provided on one batch.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when protected from light in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Ekterly 300 mg film-coated tablets are an immediate release dosage form. The film-coated tablet is yellow, 15.5 mm x 9 mm oval, biconvex and debossed with the KalVista logo 'K' on one side and the number 300 on the other side.

The aim of the pharmaceutical development was to develop an immediate-release oral dosage form that utilises standard compendial excipients and has a suitable commercial shelf-life without the need for special packaging. Furthermore, the objective was to develop a tablet of acceptable size, using a manufacturing process that is robust and reliable. This formulation has been developed for adults and adolescents, aged 12-17 years.

The risk evaluation indicated that the CQA of the finished product that had the highest risk of being impacted by the sebetralstat active substance properties and/or the excipients used in the formulation was the dissolution profile.

Sebetralstat is a crystalline active substance. The active substance particle size and solid form of sebetralstat are controlled during the synthetic process. Sebetralstat has two known true polymorphs. As indicated under the active substance section, the solid form used in the manufacture of the immediate-release film-coated tablet is form 1 which is a true, anhydrous polymorph. During the development of the tablet used in the initial Phase 1 trials and in the Phase 2 trial, a change in solid form was observed when using a wet granulation process to improve the flow of the formulation.

A study to evaluate the impact of different PSD of sebetralstat active substance on the dissolution performance of sebetralstat 300 mg immediate release tablets was performed. The data from these studies were used to support the PSD specification for the sebetralstat active substance.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards or Commission Regulation (EU) No 231/2012 for Food Additives. There are no novel excipients used in the finished product formulation. Compatibility of the excipients and the active substance has been demonstrated. All functionality related characteristics of excipients have been appropriately discussed. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The suitability of the tablet size (15.5 mm x 9 mm) for use in paediatric patients 12 years of age and older was confirmed in the clinical phase 3 trials. Oval tablets are chosen to improve swallowability.

The formulation used in the clinical trials and the intended commercial formulation has been described.

The manufacturing process development has been discussed in sufficient detail. The composition of the tablet core has remained unchanged through all clinical batches manufactured by dry granulation and has the same qualitative composition as the wet granulated product used in earlier clinical trials and showed no impact on

the dissolution profile. Tablet shape was changed from round to oval and the colour from white to yellow with similarly no impact on dissolution profile.

During the assessment, a major objection (MO2) was raised on aspects of the dissolution method relating to the selection of the medium/surfactant and its discriminatory power. A further major objection (MO3) was raised on the proposed dissolution limit as dissolution results of the clinical batch used in the pivotal efficacy study were missing. In response, the applicant provided the requested data showing that the proposed dissolution medium and level of SLS is required to achieve the critical micellar concentration and assure the performance of the dissolution method. In addition, the dissolution limit was tightened, thereby resolving the major objections.

The dissolution method is performed using dissolution apparatus with paddle mixing according to USP<711> (Type II)/Ph. Eur. 2.9.3 and using a UPLC with UV detection for analysis. Given the poor solubility of sebetralstat, the inclusion of a surfactant is required.

The discriminatory power of the dissolution method has been demonstrated with regards to the changes in the formulation, manufacturing process changes, and the active substance particle size distribution changes. A justification was provided that differences in active substance PSD may not have an impact on dissolution rate due to inherent fragility of the active substance crystals (large thin platelets) and due to attrition of the active substance crystals during the granulation and compression stages of the finished product manufacturing process.

The primary packaging is oPA/Al/PVC with aluminium lidding blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by a single manufacturer. Appropriate GMP documentation has been provided.

The manufacturing process consists of five main steps: preparing the pre-blend, dry granulation (roller compaction), granule lubrication, tablet compression and film coating of tablets. The critical process parameters and IPCs have been listed and found acceptable.

The process is considered to be a standard manufacturing process.

No validation data of the manufacturing process has been provided. The manufacturer commits to conduct prospective process validation on the first three (consecutive) production-scale batches. This is acceptable. To demonstrate the consistency of the manufacturing process, process parameters and IPCs results for the proposed commercial batch size have been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification (UPLC-UV), assay (UPLC-UV), related substances (UPLC-UV), dissolution (UPLC-UV), uniformity of dosage units (Ph. Eur. mass variation), water content (KF), and microbial limits (Ph. Eur.). The specification limits are the same for release and during shelf life.

The finished product specifications contain tests and appropriate acceptance criteria which are considered relevant for its intended use.

During the assessment a major objection (MO4) was raised regarding missing confirmatory testing for nitrosamine impurities. In response, the applicant revised the control strategy for nitrosamine impurities. The provided control strategy is accepted.

As indicated in the active substance section, the control of potential mutagenic impurities in the active substance has been developed in accordance with ICH M7. No new potential genotoxic impurities are introduced from the finished product excipients and manufacturing process and therefore the controls in place for the active substance are considered suitable for the finished product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three finished product batches using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Supportive data was provided on batches of 300 mg white, oval tablets and 300 mg and 100 mg white, round film-coated tablet batch used during development. The results met the finished product specifications in place at the time of release testing.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH), 24 months under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same specifications as for release with the addition of polymorphic form by XRPD, disintegration and tablet breaking force (hardness). The analytical procedures used are stability indicating.

No significant changes have been observed on the primary stability batches. Physical and chemical changes observed on supporting data were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

No polymorphic change has been detected in any stability programs, so this test will not be performed for any future stability studies. For future stability studies disintegration and tablet breaking force (hardness) will not be performed, however the tests will be performed as IPCs test during manufacture. This approach was found acceptable.

During the assessment, a major objection (MO5) on the primary stability batches was raised. To resolve the major objection, the applicant reduced the proposed batch size to align with the batch size of the three primary stability batches submitted by the initial submission.

Stability data on bulk tablet storage have been generated for up to 12 months in standard HDPE containers justifying the proposed hold time.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No degradation was observed for sebetralstat tablets and therefore no light protection is necessary for the tablets.

A forced degradation study was performed on the sebetralstat 300 mg white round film-coated tablets. The finished product is stable under basic conditions, high temperature and humidity and also to ambient light exposure as a solution for up to 7 days.

Based on available stability data, the proposed shelf-life of 3 years with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate used is of vegetable origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A major objection (MO1) was raised regarding the active substance manufacturing process requesting more information to provide assurance that the process is well controlled and results in consistent batch-to-batch active substance quality. In response, the applicant presented a phase 1 validation report, providing the requested data and resolving the major objection.

During the assessment, a major objection (MO2) was raised on aspects of the dissolution method relating to the selection of the medium/surfactant and its discriminatory power. A further major objection (MO3) was raised on the proposed dissolution limit as dissolution results of the clinical batch used in the pivotal efficacy study were missing. In response, the applicant provided the requested data or justifications and tightened the dissolution limit, thereby resolving the major objections.

Furthermore, a major objection (MO4) was raised regarding missing confirmatory testing for nitrosamine impurities, as there is a potential risk of presence of nitrosamine N-nitroso-diisopropylamine (NDIPA) arising

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

from the active substance synthesis. In response, the applicant revised the control strategy for nitrosamine impurities to address the risk and resolve the major objection.

A major objection (MO5) was raised on the scale of the finished product primary stability batches. In the initial submission, the applicant provided stability data on primary batches which were smaller than the proposed production batch size. To resolve the major objection, the applicant reduced the proposed batch size to align with the batch size of the three primary stability batches submitted by the initial submission.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Sebetralstat (also referred to as KVD900) 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. It is a potent, competitive, reversible inhibitor of human PKa, which reduces release of bradykinin, the mediator of oedema in HAE attacks. Sebetralstat is intended to be taken by patients at the earliest recognition of an attack.

All safety pharmacology and pivotal/definitive toxicity studies were carried out in full compliance with Good Laboratory Practice (GLP) regulations.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Several *in vitro* studies have been carried out to demonstrate sebetralstat's proof of concept.

Affinity of sebetralstat for human PKa was demonstrated in an isolated enzyme assay, with a Ki of 3.02 nM ± 0.33. Based on the parallel rightward shift in the activity curve in the presence of increasing concentrations of inhibitor with no decrease in the maximal rate (V_{max}), it could be concluded that sebetralstat behaves as a reversible competitive inhibitor. The residence half-life in the active site was 4.754 sec ± 0.643. These kinetic parameters suggest that sebetralstat is a fast-acting inhibitor which associates and dissociates very quickly from the PKa enzyme.

Further *in vitro* studies were carried out using a fluorogenic peptide or the endogenous target HK as substrate for PKa, in diluted or undiluted activated human plasma:

- The activity was tested on plasma from healthy subjects and HAE subjects, with comparable IC_{50} values concerning enzyme inhibition
- Concentrations of 200-300 nM were generally required for effective inhibition of endogenous HK substrate cleavage on undiluted plasma
- Inhibition of PKa demonstrated (via an increase in substrates and a decrease in products of this enzyme) in a study on *in vitro* activated plasma from healthy volunteers given 600 mg sebetralstat PO. Inhibition up to 10h post-treatment
- A minimum concentration of 50 nM is required *in vitro* for significant inhibition of HK cleavage in the plasma of healthy volunteers vs. 100 nM in that of HAE patients. This may be attributed to the fact that in the plasma of healthy subjects, the endogenous mechanism (absent in HAE subjects) helps to inhibit this cleavage
- Dose-dependent inhibition demonstrated *in vitro*
- Suppression of positive feedback activation of the KKS (by reducing FXIIa generation and PK cleavage) has been achieved in activated plasma from healthy volunteers up to 6h after PO administration of sebetralstat at a dose of 600 mg
- Several *in vitro* studies on plasma from mice, rats, rabbits, dogs, pigs and monkeys have demonstrated that monkeys (IC_{50} = 5.07 nM), mice (IC_{50} = 13.9 nM), and rats (IC_{50} = 69.8 nM), are pharmacologically relevant species. After PO administration of sebetralstat in rats and NHP (+ IV in NHP), followed by *in vitro* plasma stimulation with EA, monkeys were shown to be the most suitable model (NHP: IC_{50} (PO and IV) = 1.75 nM, IC_{50} (powder in capsule) = 3.2 nM; rat: IC_{50} = 152 nM)
- A single *in vitro* study was carried out, representing the conditions of clinical use of the treatment, with plasma stimulation prior to treatment with sebetralstat. The curves show a reduction in enzymatic activity from a concentration of 300 nM. The significance of the results is not discussed. No justification is given for the administration of treatment prior to plasma activation in the other studies.

One in vivo efficacy study of sebetralstat has been carried out, in which the anti-inflammatory activity was measured in a rat model of carrageenan-induced paw oedema (CPE). Since there is no established animal model of HAE, the CPE model was selected as a surrogate for tissue swelling in HAE attacks. CPE model involves different inflammatory pathways, including kinins and was selected by the applicant to demonstrate pharmacological engagement of the target. Male rats were orally administered with sebetralstat at doses of 30, 100 and 300 mg/kg, and one hour after dosing, animals were injected with carrageenan into the right hind paw. In this study, 300 mg/kg significantly reduced inflammation at 6h post-induction (7h post-treatment), at the same level as the positive control used, indomethacin. The 30 mg/kg dose appears to have achieved a better reduction in inflammation at 2 and 4h post carrageenan than 100 mg/kg, demonstrating that response to treatment is not dose-dependent in this study.

2.5.2.2. Secondary pharmacodynamic studies

The off-target effects of sebetralstat were studied on several serine proteases (protease family of its target PKa) as well as on other enzymes, receptors and transporters from different species (rat, rabbit, guinea pig,

pig, bovine, human). No inhibition greater than 50% was observed at 10 µM. Sebetralstat was shown to be selective for its target with a selectivity window greater than 1656-fold.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were carried out in rats and NHP, two pharmacologically relevant species. These GLP-studies assessed the effect of sebetralstat on cardiovascular, nervous and respiratory systems.

With regard to the cardiovascular system, an in vitro study on hERG channels demonstrated the absence of inhibition > 30% of these channels at a concentration of 30 µM. This concentration allows a safety margin > 50. When NHP was exposed to doses up to 300 mg/kg, no effect was observed on heart rate, BP and ECG parameters, QTc prolongation and other waveform morphologies. At this dose, the margins are 1.8 and 1.1 for AUC and C_{max} respectively (margins adjusted for free fraction).

The central nervous system study was conducted in rats and revealed no particular toxicity. With regard to the respiratory system, the rat study revealed no change in respiratory parameters. In these two studies, rats were exposed to doses up to 1000 mg/kg, allowing safety margins of 4.2 and 0.7 in relation to AUC and C_{max} respectively.

2.5.2.4. Pharmacodynamic drug interactions

N/A

2.5.3. Pharmacokinetics

Determination of sebetralstat in various formulations (20% TPGS in water formulations, DMSO formulations, 0.5% w/v HPMC in water) and in plasma from mouse, rat, rabbit, dog and NHP was performed using either LC-UV or LC-MS/MS methods. Validated analytical methods were used for analysis of GLP mouse, rat, rabbit, dog and NHP TK samples from GLP-compliant repeat dose toxicology, reproductive toxicology and carcinogenicity studies. Information provided on the analytical methods is considered sufficient.

Sebetralstat demonstrated moderate intestinal permeability in vitro, with an apparent permeability (P_{app}) value of 9.0 × 10-6 cm/s in Caco-2 cells.

PK studies, using LC-MS/MS to measure sebetralstat in plasma, were conducted in mice, rats, rabbits, dogs and NHPs using single i.v. and/or oral doses of sebetralstat. These in vivo studies across multiple species revealed rapid absorption of sebetralstat after oral administration. The apparent bioavailability was generally moderate but showed variability among different doses and formulations tested. In mice, the bioavailability ranged from 27% to 28.7%, with a time to maximum concentration (T_{max}) of 0.25 to 0.83 hours. Rats exhibited a bioavailability range of 23.3% to 78.6%, with a T_{max} of 0.5 to 1.67 hours. However, when administered at a high dose of 300 mg/kg in rats, the bioavailability increased to 166.7% with a T_{max} of 5.33 hours, suggesting saturation at this high dose. In non-human primates (NHPs), the bioavailability ranged from 21.7% to 48.4%, with a T_{max} of 0.5 to 2 hours. In rabbits, although sebetralstat was not administered intravenously and thus apparent bioavailability was not measured by the applicant, the drug was still rapidly absorbed with a T_{max} of 1 to 2 hours.

Generally, plasma exposure increased proportionally with dose after single-dose administration of sebetralstat, although there is evidence of non-linear pharmacokinetics. At higher doses in rats, supra-

proportional increases in AUC were observed across the 10-300 mg/kg dose range. In NHP, based on the 1 and 10 mg/kg oral liquid single doses, exposure of sebetralstat did not increase in a proportional manner with a 10-fold increase in dose, with C_{max} increasing 19-fold and AUC_{0-inf} increasing 16-fold, but following single administration of 10 and 100 mg sebetralstat powder in capsule, exposure increased in a proportional manner. In non-human primates (NHPs), no consistent gender-based differences in plasma exposure were observed between males and females, however, individual data in study reports (e.g. the 26-week repeat-dose study) suggest a notable inter-individual variability. The results in rats revealed a more complex pattern: after a single dose, female rats typically exhibited higher exposure levels compared to males. Upon repeated dosing, male rats showed an increase in exposure. By the final TK sampling occasion, the difference in C_{max} and AUC between male and female rats was generally less than 2-fold. A similar pattern was observed in transgenic mice after repeated dosing in the 26-week carcinogenicity study.

In all species, following i.v. administration of 1 mg/kg sebetralstat in 10% DMSO/10% Cremophor ER/80% sterile water, sebetralstat exhibited a moderate clearance (moderate to high in NHP), a volume of distribution close to body water volume, or slightly above (~2-fold in NHP), and a consistently short elimination half-life (0.33-1.03 hour).

Regarding the distribution, sebetralstat rapidly distributed in all tissues. The majority of maximum tissue and concentrations decreased markedly at 4 and 8 hours post-dose. With the exception of liver, kidney and adrenal gland, radioactivity was not quantifiable in tissues by 72 hours post dose. The highest tissue concentrations were measured in the liver, kidney and adrenal structures and the bladder wall. The radioactivity in central nervous system was very low and levels of radioactivity in the gastrointestinal tract walls reflected the passage of the oral dose.

The extent of placental transfer of total radioactivity was investigated in rats (study 187593) by QWBA where limited placental transfer was observed.

Moreover, data suggest a moderate binding affinity of sebetralstat for melanin.

Plasma protein binding was assessed in the plasma of all animal species tested and of humans. Mean fraction unbound was approximately 6% in mice, 4% in rats, 13% in rabbits, 34% in dogs, 38 % in NHPs and 23% in humans.

The mean blood to plasma ratio values calculated suggests limited partitioning of sebetralstat into red blood cells in all species (Mouse: 0.60, rat: 0.56, dog: 0.80, pig: 0.93, NHP: 0.9, Human: 0.8).

Regarding metabolism of sebetralstat, in vitro intrinsic clearance (CLint) in hepatocytes from various species resulted in significant variation across species. HW rats, used in toxicology studies, had notable higher clearance than human (72.4 vs. 8.0 µL/min/106 cells), while NHP had a lower clearance at less than 3 µL/min/106 cells. At 5 µM, all 18 metabolites observed in human hepatocytes in vitro were also detected in rat and NHP hepatocytes.

In vivo, sebetralstat is extensively metabolised. CYP3A4 (mainly) and CYP2C8 (to a substantially lower extent), were the major enzymes responsible for the in vitro metabolism of sebetralstat, with CYP2B6 and CYP2E1 also contributing to some extent. After dosing 600 mg of [14C]-sebetralstat orally to human subjects, sebetralstat was the predominant component in plasma (64%). [14C]-sebetralstat was also predominant in NHP (21-25.9%) and rat (83.4-95.4%) plasma after oral administration. No metabolite accounted for a mean of >10% of drug-related material in the AUC_{0-24} across subjects. The most abundant plasma metabolites were the cleavage products M19 and M10 (mean of 7.10% and 4.00% of AUC_{0-24} respectively) and the pyridyl desmethyl product M3 (mean of 4.01% of AUC_{0-24}). Although there was

extensive biotransformation to a variety of metabolites, sebetralstat was the main drug-related component in urine and feces (mean of 8.66% and 12.5% respectively across subjects).

Following in vivo screening studies in humans, rats and NHPs, all characterised metabolites were present at a similar or greater abundance in NHP plasma compared with human. All characterised metabolites were present at a similar or greater abundance in rat plasma compared with human with the exception of M1, M2, M11 and, M13 (which were present, but at lower circulating levels).

The plasma exposure of M19 (KV124020; the most abundant metabolite identified in human plasma) was also determined in rat and NHP plasma obtained from sebetralstat repeat dose toxicology studies. In rats (Study 8463718), sex differences in M19 mean C_{max} and AUC_{0-24} values were greater than 2-fold, with substantially higher exposure observed in males compared to females. AUC_{0-24} values in males were 16-, 10- and 5-fold higher compared to females after dosing 30, 100 and 300 mg/kg of sebetralstat, respectively. In contrast, rat plasma samples were taken from pivotal GLP study 8418576 (26-week toxicology study) where higher sebetralstat exposure was observed for females. More specifically, following 300 mg/kg oral dose of sebetralstat, the AUC ratio of M19 and sebetralstat was 0.9% for males and 0.16% for females. The observed gender-related differences in metabolite exposure are primarily attributed to differences in hepatic enzyme expression between male and female rats. Given that M19 represents a negligible proportion of the circulating drug-related material and is not pharmacologically active, these sex differences in metabolite exposure would not affect the overall interpretation of the toxicology studies in rats.

In addition, in NHPs study (8463724), the exposure to metabolite M19 was determined in plasma obtained from 13-week intermittent toxicology study (8420897). Those NHPs were found to be positive for hepatitis. Pharmacokinetic analysis showed consistency in the drug exposure between the 13-week and 26-week studies (both intermittent dosing), indicating that the HAV infection did not affect the pharmacokinetics of sebetralstat.

Regarding elimination of sebetralstat, total radioactivity was rapidly eliminated in both toxicology species, mainly via the feces, with this route accounting for a mean of 91% in rats and of 82% in NHPs, by 168 hours post-dose. The total mean recovery of radioactivity was almost complete with 99% in rats and 95% in NHPs measured by 168h post-dose. In humans, a greater proportion of the radioactive dose (32%, from a mean total excreta recovery of 96%) was recovered in urine in humans, with a mean of 8% of the dose as unchanged sebetralstat. Given that faecal excretion of radioactivity in humans was 2-fold higher than in urine, and that drug-related material was excreted mainly as metabolites, this indicates that the clearance was mainly by hepatic metabolism with elimination of metabolites primarily via bile into the faeces; clearance occurs to a lower extent via urine. This is supported by results obtained after dosing [14C]-sebetralstat orally to bile duct-cannulated male rats, where a mean of 55% of radioactivity was recovered in bile up to 48 hours post dose, mainly as metabolites.

Sebetralstat was secreted in the milk of lactating rats with mean milk:plasma ratio of total radioactivity between 1.14 and 1.17 over the sampling period. Radioactivity rapidly decreased with mean level close to background at 24h post-dose (<50-fold level detected at 1h post-dose).

Pharmacokinetic drug interaction of sebetralstat was investigated in vitro. Direct inhibition of CYPs 2C9 and 3A4 by sebetralstat was observed with IC_{50} values of 30.1 µM (CYP2C9), 120 µM (CYP3A4 testosterone substrate) and 121 µM (CYP3A4, midazolam substrate). No time-dependent inhibition of CYP2 2C9 or 3A4 was observed. There was no inhibition of CYPs 1A2, 2B6, 2C9, 2C19 or 2D6. Sebetralstat was not an inhibitor of UGT1A6 or UGT2B7 (IC_{50}>100 µM) but was a weak inhibitor of UGT1A1, UGT1A3, UGT1A4 and UGT1A9. Induction of the expression of CYPs 2B6 (in 2 out of 3 donors exposed), 2C8 (3 donors), 2C9 (2/3 donors)

and 2C19 (1/3 donors) was observed at 100 µM sebetralstat, while expression of CYP3A4 was found to be induced by sebetralstat in a dose dependant manner from 10 µM. Sebetralstat did not show any induction of CYP1A2 expression. Sebetralstat caused no dose-dependent inhibition of OAT1 at concentrations up to 100 µM. Sebetralstat caused inhibition of all other transporters over the concentration range studied, with IC_{50} values of 19.2, 5.28, 8.05, 7.76, 86.3 and 51.3 µM against OAT3, OCT2, MATE1, MATE2-K, OATP1B1 and OATP1B3 respectively. No time-dependent inhibition of OATP1B1 or OATP1B3 was evident. Sebetralstat did not inhibit P-gp up to 100 µM but was a weak inhibitor of BCRP and BSEP. Sebetralstat was not a substrate for both BCRP and P-gp in vitro. The interpretation of these results in light of drug-drug interaction guidance is discussed in the Clinical part of the dossier.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity study has been reported by the applicant. General acute toxicity information can be obtained from the GLP repeat-dose toxicity studies in rats and NHP.

2.5.4.2. Repeat dose toxicity

To support the marketing authorisation, the applicant performed GLP-compliant repeat-dose studies in Crl:WI(Han) rats and in Cynomolgus NHP via oral route for up to 26 weeks.

The dog was initially considered as a non-rodent species, however, due to poor clinical condition of some animals in a 28-day repeat-dose study associated with changes in the alimentary tract that were unrelated to treatment, and due to the absence of histopathological findings to account for the poor clinical condition, the dog was considered as inappropriate. Moreover, the choice of NHP as a non-rodent species is also supported by pharmacology data showing a more relevant affinity of sebetralstat for human PKa.

Prior to these studies, non-GLP studies to determine MFD followed by a 7-day fixed repeated dose periods were performed in both species:

- In rats, the daily administration of sebetralstat at doses up to 1,000 mg/kg/day for seven days was well tolerated with no unscheduled deaths. Minimal/slight microscopic changes were apparent in the liver, kidneys, and adrenals. These changes were either considered to be male rat specific (hyaline droplets in the kidneys) or reversible in nature and therefore 1,000 mg/kg/day was considered acceptable for the high dose on longer term studies.
- In the NHP study, administration of sebetralstat to NHPs in the MTD phase was well tolerated; extended clotting times were apparent at 1,000 mg/kg/day (500 mg/kg bid). In the 7-day fixed-dose phases, treatment with sebetralstat at 100 or 300 mg/kg/day was generally well tolerated in-life although some effects on the liver (changes in liver enzymes, bilirubin and hepatocellular vacuolation) were evident in a dose-dependent manner.

In addition, bridging studies were conducted in rats and NHPs to support the change of vehicle from 20% TPGS to 0.5% HPMC. Those studies were considered to support this change as no adverse findings were observed up to the highest doses tested (300 mg/kg/d in rats, 100 mg/kg/day in NHPs) leading to comparable or higher exposure than in the 1-month studies in both species at the same dose levels.

Regarding rats studies:

- In the 28-day study, daily oral gavage administration of 30, 100, 300, or 1,000 mg/kg/day sebetralstat to Crl:WI(Han) rats was clinically well tolerated in all animals. Body weight gain was reduced for males but slightly increased in females at ≥300 mg/kg/day sebetralstat. Liver, thyroid/parathyroid (females only), adrenals, kidney, spleen, ovaries and heart weights were increased at 1,000 mg/kg/day and were higher for the adrenals of males and the liver, kidney and spleen of females at 300 mg/kg/day. Microscopic changes were apparent in the liver, thyroid, adrenals, pituitary gland, kidneys, mammary gland, salivary gland, spleen, ovaries and vagina at 300 or 1,000 mg/kg/day, with evidence of an ongoing recovery at the end of the 4-week treatment-free period. The findings were considered adverse in animals administered 1,000 mg/kg/day but not at 300 mg/kg/day due to their nature and severity as most relevant findings at this dose were minimal or slight hypertrophy in the liver and adrenal glands, considered to be adaptive responses in the absence of any significant cellular damage or evidence of functional disturbance. Thus, the NOAEL was 300 mg/kg/day, corresponding to exposures on Day 28 of the dosing phase of C_{max} and AUC_{0-24} values of 145,500 ng/mL and 864,500 h.ng/mL respectively, for males and females combined.
- In the 13-week study, rats were administered daily oral dose of 0, 30, 100 and 300 mg/kg/day. Sebetralstat was clinically well tolerated, with no sebetralstat-related deaths. Reduced body weight gains were observed in males at 300 mg/kg/day and in both sexes during the first 2 weeks of the recovery. Haematological changes included slightly higher reticulocyte counts (females at 100 mg/kg/day and both sexes administered 300 mg/kg/day), low mean cell haemoglobin concentration, high red cell distribution width (females at 300 mg/kg/day), and high total white cell counts, and shorter prothrombin times (males ≥100 mg/kg/day). Clinical chemistry changes were limited to minimally higher cholesterol (at 300 mg/kg/day) and minimally lower total protein and albumin concentrations (females ≥30 mg/kg/day). Histopathological changes were seen in the adrenal, liver, ovary, and kidneys and were correlated with higher organ weights (all), macroscopic observations (adrenal), or plasma electrolyte and urine changes (kidney). All changes observed were considered non-adverse due to their minimal nature and recovery. It should be noted that in this study, spleen, mammary gland, pituitary gland and thyroid were not target organs, contrary to the results observed the previous 28-day study, indicating that these changes were likely adaptive. The NOAEL was thus determined to be the highest dose, 300 mg/kg/day, corresponding to Day 85 sebetralstat C_{max} and AUC_{0-24} values of 83,900 ng/mL and 697,000 h.ng/mL respectively, for males and females combined.
- In the 26-week study, daily oral gavage administration of 30, 100, or 300 mg/kg/day was clinically well tolerated, with no sebetralstat-related deaths. The administration of sebetralstat resulted in minimal and transient effects on body weight gains correlated to food consumption (low in males, high in females) and on body weight (males only) at 300 mg/kg/day. Other changes observed were ovary interstitial cell vacuolation of low incidence and severity, and tubule cell hypertrophy or reduced accumulation of hyaline droplets in the kidney that correlated with minimal in-life and clinical pathology changes at 300 mg/kg/day. Adrenal cortical vacuolation, liver hepatocyte hypertrophy, and thyroid follicular cell hypertrophy were also reported at 100 or 300 mg/kg/day. The sebetralstat-related findings in the adrenal, liver, and thyroid were considered most likely to be adaptive or stress related in the absence of adverse in-life changes and due to the nature and low severity of these findings. Transient haematological effects were noted but were minimal and transient and did not correlate with histopathological findings. Therefore, all findings in the 26-week study were considered non-adverse. Thus, the NOAEL was 300 mg/kg/day, the highest dose tested, which corresponded to C_{max} and AUC_{0-24}

values of 96,400 ng/mL and 983,000 h.ng/mL respectively, for males and females combined at Week 26. No recovery group were included. This is acceptable according to ICH M3 (R2) Q&A.

Regarding NHP studies:

- In the 35-day study, daily oral gavage administration of 0, 50, 100, 300 and 500 mg/kg/day sebetralstat led to poor tolerability in the 500 mg/kg/day dose group. The dose was reduced to 300 mg/kg/day from Day 17. At dose levels ≥ 300 mg/kg/day, three animals in total were humanely killed early due to poor conditions, mainly a consequence of adverse effects in the liver (evidenced by macroscopic and microscopic liver changes and chronically elevated enzyme levels). Microscopic evidence of hepatotoxicity was not detected at 50 and 100 mg/kg/day. However, biochemical evidence of hepatic injury (increased ALT, GLDH, GGT and AST) was noted in animals administered 100 mg/kg/day. All liver enzyme abnormalities resolved during the recovery period. Microscopic findings in adrenals, kidneys and thymus were also apparent at sebetralstat 500/300 or 300 mg/kg/day. All changes observed at the high dose level had resolved at the end of the 28-day recovery period. In addition, reduced food consumption, soft/liquid faeces and emesis correlating with decreased body weight, were seen in males administered 100 mg/kg/day and considered as adverse as it slightly exceed normal variation for this species. Therefore, the NOAEL was determined at 50 mg/kg/day and was based on findings including reduced body weight and a trend in raised liver enzymes. This corresponded to C_{max} and AUC_{0-24} values of 2,800 and 8,160 h.ng/mL, respectively, for males and females combined.
- In the 13-week study with daily oral (gavage) dose of 0, 10, 25 or 50 mg/kg/day, sebetralstat was well tolerated with no related effects observed on survival, clinical observations, feces, body weights, organ weights, food consumption, menstrual cycle, ophthalmoscopy, ECG, blood pressure, haematology, coagulation, or urinalysis parameters. Clinical pathology assessments showed increased liver enzyme values (GLDH, ALT, and AST), with correlating adverse microscopic findings of increased mononuclear cell infiltrates in the liver at all dose levels, as well as hepatocellular degeneration and necrosis in one female administered 50 mg/kg/day. Increased mononuclear cell infiltrates in the liver at ≥10 mg/kg/day were reported as adverse by the study pathologist. However, given the low severity of the microscopic findings and the lack of functional impact on indicators of liver function, the applicant commissioned an independent review by a Pathology Working Group formed by 5 experienced histopathologists, to independently review the slides of the liver sections of the study. The independent PWG concluded that daily administration of KVD900 at dose levels of up to 50 mg/kg/day for 13 weeks was not associated with any adverse histopathology findings in the liver of monkeys. Accordingly, the NOAEL in the study was confirmed to be 50 mg/kg/day. This corresponded to C_{max} values of 2,160 and 2,080 ng/mL (2,120 ng/mL, combined) for males and females, respectively, with associated AUC_{0-24} values of 7,390 and 6,630 h.ng/mL (7,010 h.ng/mL, combined).
- In a second 13-week study, NHP were administered sebetralstat by oral gavage 0, 50, 100, 200 and 300 mg/kg/dose sebetralstat, twice weekly (Mondays and Fridays). sebetralstat was well tolerated with no unscheduled death up to the highest dose tested. Mildly to markedly increased values of hepatocellular enzymes (ALT, GLDH and/or AST) activities were observed at one or more time points during the study, including in some animals during the pre-dose phase and also in individual control animals during study phases. A PCR analysis determined copies of Hepatitis A virus RNA in 20/42 animals.
- In the 26-week study, NHP were also administered sebetralstat by oral gavage 0, 50, 100, 200 and 300 mg/kg/dose sebetralstat, twice weekly (Mondays and Fridays). Sebetralstat was well tolerated at

all dose levels in both males and females. There were no sebetralstat-related clinical observations or changes in any clinical chemistry parameter. All microscopic findings were sporadic in incidence with no relation to dose and were considered incidental and of common nature with similar incidence and severity in control and dosed animals. It should be noted that there was no histopathological finding in the liver such as mononuclear cell infiltration or hepatocyte degeneration which were seen in previous studies in the NHP.

2.5.4.3. Genotoxicity

A complete package of *in vitro* (a bacterial mutagenicity assay and a mouse lymphoma cell assay) and *in vivo* (micronucleus test in rats) genotoxicity studies was conducted. The designs tests were based on appropriate OECD test guidelines and in accordance with ICH S2 (R1) and ICH M3 (R2) guidelines. In the *in vitro* bacterial reverse mutation assay, sebetralstat was negative in *Salmonella* test strains in both presence and absence of metabolic activation. In the *in vitro* mouse lymphoma cell assay, sebetralstat did not induce mutation at the *tk* locus of when tested up to the limit of cytotoxicity (450 µg/mL, equivalent to 0.92 mM), in absence or presence of metabolic activation. The *in vivo* rat bone marrow micronuclei assay was part of the 28-day oral repeat-dose toxicity study conducted in rats. Sebetralstat did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male or female treated up to 1000 mg/kg/day.

2.5.4.4. Carcinogenicity

The potential carcinogenicity of sebetralstat has been evaluated in accordance with guidance ICH S1B, in a pivotal 26-week oral dose study in the transgenic mouse, (CbyB6F1/Tg(HRAS)2Jic) and a 104-week, oral dose, carcinogenicity study in rats. 10-day and 28-day repeat dose studies in mice and a 13-week repeat dose study in female rats were conducted to support the dose level selections for these pivotal carcinogenicity studies.

Regarding the 104-week carcinogenicity study, administration of sebetralstat during the lifespan of rats did not impact survival. No test-item-related increase in the incidence of malignant neoplasms was noted. Sebetralstat administration was associated with some increases in benign tumours in the female livers, male pituitary and thyroid glands, testes and ovaries. These changes were considered by the applicant as common in this strain and/or a consequence of altered endocrine hormone metabolism associated with xenobiotic-induced liver enlargement and enzyme induction and, therefore, are not relevant to humans.

In the 26-week study in wild-type CByB6F1 Tg(HRAS) mice, a dose-related trend of bronchioloalveolar adenoma and bronchioloalveolar, adenoma/carcinoma were noted across all groups, but the incidences of these findings were within the Testing Facility historical control ranges and therefore considered to be inconsequential. Sebetralstat-related effects were considered limited to the liver (increased liver weight and minimal centrilobular hypertrophy) at 200 mg/kg/day in males and 300 mg/kg/day in females.

2.5.4.5. Reproductive and developmental toxicity

A full set of developmental and reproductive toxicity studies were performed in rats and rabbits.

Sebetralstat at doses up to 600 mg/kg/day did not induce any adverse effect on either male or female rat fertility, as well as sperm parameters. The NOAEL for male and female fertility was 600 mg/kg/day

corresponding to exposure multiples >40-fold based on total AUC levels, and 6.9 (males) and 8.3 (females) based on unbound AUC levels.

In embryofetal development toxicity studies, treatment of rats during organogenesis with sebetralstat induced malformations (mostly cleft palate and ventricular septal defects) and embryofetal lethality at the dose 600 mg/kg/day. Non-specific maternal toxicity was also observed at this dose level, i.e. body weight loss, reduced body weight gain and food consumption, but a causal relationship with developmental toxicity has not been demonstrated. The developmental NOAEL was 300 mg/kg/day in rats, corresponding to a safety margin of 3.0-fold based on unbound AUC levels. In contrast, no drug-induced malformation or embryofetal lethality was observed when female rabbits were treated during organogenesis at up to 300 mg/kg/day, corresponding to 6.8-fold human exposure based on unbound AUC levels. Maternal toxic effects were reported at this dose level (body weight loss, reduced body weight gain and food consumption), and were the most probable cause of the observed decrease in fetal weights and delayed ossification in fetuses of this group.

In the rat pre- and postnatal development toxicity study, there was a decrease in the body weight gain during the whole lactation period (7-8% from PND 1-21) which persisted during the postweaning period in F1 males only (6% from week 0 to 10) with a slight impact on terminal body weight (7% decrease on week 10). However, these findings are likely of no toxicological relevance in the absence of any treatment-related effect on any monitored preweaning developmental landmarks (pinna detachment, eye opening, static righting reflex, startle response, pupillary light reflex), sexual maturation, neurobehavioural examinations, and reproductive performance. Therefore, the NOAEL for pre -and post-natal development was determined at 450 mg/kg/day. TK was not determined in that study and exposure multiples cannot be determined on the basis of exposure levels measured in the rat EFD study performed at 100, 300, and 600 mg/kg/day.

A preliminary 3-week toxicity study was conducted in 22-day-old juvenile rats as a dose-ranging study for a potential pivotal study to support proposed future administration in paediatric subjects from 2 to 11 years of age. Sebetralstat was generally well-tolerated at doses up to 1000 mg/kg/day. In line with the PIP for sebetralstat, additional JAS are not deemed necessary to support the current application in children from 12 years of age.

2.5.4.6. Toxicokinetic data

Toxicokinetic data were discussed with the pharmacokinetics section.

2.5.4.7. Local tolerance

No local tolerance studies were performed as sebetralstat is intended to be administered via oral route.

2.5.4.8. Other toxicity studies

Studies on impurities:

Two impurities were investigated for genotoxicity potential by the applicant. For both impurities a bacterial reverse mutation assay and an in vitro mammalian cell micronucleus assays were performed. Those tests were performed in compliance with GLP a relevant OECD guidelines (n°471 and 487). For one impurity, bacterial reverse mutation assay was negative up to the highest recommended dose of 5000 µg/plate in the presence and absence of metabolic activation. In addition, the in vitro micronucleus assay concluded that the

impurity was neither clastogenic nor aneugenic up to 354 µg/mL in the presence or absence metabolic activation. For the second impurity, bacterial reverse mutation assay was also negative up to the highest recommended dose of 5000 µg/plate in the presence and absence of metabolic activation. The in vitro micronucleus assay also concluded to the absence of clastogenic or aneugenic potential for the impurity up to 354 µg/mL in the presence or absence metabolic activation

Phototoxicity:

Photo-safety was evaluated using a stepwise approach according to ICH Guidance S10 on photo-safety Evaluation of Pharmaceuticals. Sebetralstat has been shown to absorb light within the natural light range (290-700 nm), with the highest absorbance being observed at 303 nm. The molar extinction coefficient (MEC) expressed at the lambda maxima 303 nm is approximately 5824 litres per mole per cm when tested at 20 µM in methanol and therefore exceed the limit of 1,000 L/mol/cm set in ICH S10. Thus, the applicant conducted two non-GLP ROS assays using both superoxide anion and singlet oxygen. However, due to precipitation at concentrations higher than 20 µM, results are inconclusive. In line with ICH S10 and GLP, the applicant performed a 3T3 NRU-PT. No cytotoxicity was observed.

Studies on excipients:

No dedicated toxicology studies are mandatory for excipients considering no novel excipients are used.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): Sebetralstat				
CAS-number (if available):				
PBT screening		Result		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.47±0.02 (25±1°C)		Potential PBT: N
PBT-assessment –				
Parameter	**Result relevant for conclusion**			**Conclusion**
Bioaccumulation potential- log K_{ow}	log K_{ow}	1.47±0.02 (pH7)		not B
Persistence	DT50	$DT_{50\ Total\ System}$ (12 °C) 203 d / 589 d		vP
Toxicity	NOEC or CMR			T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB			
Phase I				
Calculation	**Value**		**Unit**	**Conclusion**
$PEC_{sw,\ refined}$	0.017		µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)				N (to be argued)
Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		**Remarks**
Adsorption-Desorption Soil 1 = Clay loam (Kenslow, 2.9% OC)) Soil 2 = Loamy sand (Speyer 2.1, 0.6% OC)	OECD 106 OPPTS 835.1110	$K_{oc,\ soil\ 1}$ =953.66 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 1838.47 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 22625.91 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 111.05 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 86.34 L/kg_{oc}		Kd values are 27.66, 11.03, 248.89 L/kg respectively for soils 1, 2 and 3.

Soil 3 = Clay (La Reina, 1.1% OC) Sludge 1 = Burly Menston (37.2% OC) Sludge 2 = Harrogate South (37.9% OC)					NB: Adsorption is not driven by %OC but rather soil clay content.
Ready Biodegradability Test	OECD 301B	Not readily biodegradable 0.7-3.03% degradation after 28 days			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Silt loam (Calwich Abbey) Sediment 2 = sand (Middle Pond)	OECD 308	$DT_{50, water}$ = 6.61 / 6.11 d $DT_{50, sediment}$ = no notable decrease $DT_{50, whole\ system}$ = 95.6 / 277 d And 168 / 2980 when including non-extractable residues shifting to sediment 55.8 % (day 14, 48.7%parent + 7.1%NER, sed1) 77.4 % (day 14, 65.5%parent + 11.9%NER, sed2) $^{14}CO_2$ = 0% NER 100 DAT = 15.5% (sed1) and 20% (sed2) Transformation products >10% = 1 TP1 = 32.8% at 100 DAT for sed1 (2,6% for sed2) DT50 M1: no notable decrease			Dissipation from water is fast, paralleled by a transfer to sediment. No mineralisation was observed TP1:Pyrazole-desmethyl-KVD900 (HPLC, RT: 20 min), (IUPACname: N-[(3-fluoro-4-hydroxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-[[4-[(2-oxopyridin-1-yl)methyl]phenyl]methyl]pyrazole-4-carboxamide)
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata (strain 278/4)*	OECD 201	NOEC / EC_{10}	≥100 / >100	mg/L	For both growth rate and yield
Daphnia magna, Reproduction Test (Clone from MicroBio Tests Inc.)	OECD 211	NOEC / EC_{10}	≥10 / >10	mg/L	juvenile production
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC / EC_{10}	≥10 / >10	mg/L	For all endpoints Hatching success, post-hatch survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC / EC_{10}	≥1000 / >1000	mg/L	respiration
Chironomus test / *Chironomus riparius (strain from Symaris and Blades Biological)*	OECD 218	NOEC / EC_{10}	250 / 313	mg/kg	Adult emergence.
Phase IIa Risk Characterisation					
Environmental compartment	**PEC** µg/L	**PNEC** *mg/L*	**PEC/PNEC**	**Trigger value**	**Conclusion**
Surface water	0.0171	1	$1.71x10^{-5}$	1	acceptable risk
Groundwater	0.00428	1	$4.28x10^{-6}$	1	acceptable risk
STP Microorganisms	0.0171	100	$1.71x10^{-7}$	0.1	acceptable risk

Sediment	0.0414 mg/kg dry weight	2.5 mg/kg dry weight	0.0166	1	acceptable risk
Phase IIb Studies: not required					

2.5.6. Discussion on non-clinical aspects

Several *in vitro* studies and one in vivo study were conducted with sebetralstat to demonstrate its proof of concept in the treatment of HAE attacks. Sebetralstat demonstrated good affinity for human PKa using an isolated enzyme (Ki = 3.02 nM) and was shown to be a reversible competitive and fast-acting inhibitor. When measuring blockade of HK cleavage (endogenous substrate for PKa), concentrations in the range from 50 to 300 nM were generally required for effective inhibition of PKa in undiluted activated plasma from healthy subjects and HAE patients. In activated plasma from healthy volunteers administered oral sebetralstat at a dose of 600 mg, PKa inhibition was observed up to 10h after dosing, while reduced FXIIa generation and PK cleavage were still present at 6h post treatment. Therefore, by inhibiting PKa, sebetralstat not only blocks cleavage of HK, but also suppresses positive feedback activation of the KKS.

However, only one *in vitro* study was performed to mimic the conditions of clinical use, with plasma stimulation prior to treatment with sebetralstat. Reduction in PKa activity from a concentration of 300 nM was observed.

In the absence of sufficient animal model of HAE, an in vivo study has been carried out in rats, using the model of general inflammation (CPE model). The CPE model involves different inflammatory pathways, including kinins and was selected to demonstrate pharmacological engagement of the target. In this study, sebetralstat at a dose of 300 mg/kg significantly reduced inflammation at 6h post-induction (7h post-treatment), to the same extent as the positive control used. The 30 mg/kg dose appears to have achieved a better reduction in inflammation at 2 and 4h post carrageenan than 100 mg/kg, demonstrating that response to treatment is not dose-dependent in this study. The same was observed clinically, no notable difference in efficacy between doses of 300 and 600 mg. Sebetralstat was administered 1h before carrageenan stimulation, which again does not represent the clinical conditions of use. This pattern of administration would correspond to a preventive indication rather than an acute treatment. In addition, carrageenan is administered 1h after sebetralstat treatment, which for certain doses corresponds to T_{max} or post-T_{max} (except for the 300mg/kg dose). After receiving the answers to the questions, the data provided to demonstrate proof of concept for sebetralstat in the treatment of HAE attacks remains very limited. Only one *in vitro* study approximately replicates the clinical administration schedule (treatment of attacks). The applicant highlights articles showing administration of icatibant (on-demand HAE drug) 15 minutes before and simultaneously with the carrageenan injection. In the context of this MA, sebetralstat is administered one hour before the carrageenan in the only in vivo study provided. The laboratory clearly states that the objective of its studies is not to serve as a treatment model for a human disease, nor to reflect clinical efficacy or the treatment schedule and that the vivo model serves to demonstrate the pharmacological engagement of the target, not to serve as a treatment model for a human disease. After discussion with the clinic, the efficacy in humans appears satisfactory. No other points are therefore raised in non-clinical pharmacology, concerning the efficacy of sebetralstat in HAE crisis treatment.

Overall, the data provided to demonstrate proof of concept for sebetralstat in the treatment of HAE attacks remains very limited. Only one *in vitro* study approximately replicates the clinical administration schedule (treatment of attacks). The applicant highlights articles showing administration of icatibant (on-demand HAE drug) 15 minutes before and simultaneously with the carrageenan injection. In the context of this MA,

sebetralstat is injected one hour before the carrageenan in the only in vivo study provided. The laboratory clearly states that the objective of its studies is not to serve as a treatment model for a human disease, nor to reflect clinical efficacy or the treatment schedule but that the vivo model serves to demonstrate the pharmacological engagement of the target. Given the clinical efficacy in humans appears satisfactory, no other points are therefore raised in non-clinical pharmacology concerning the efficacy of sebetralstat in HAE crisis treatment. Pharmacology studies sufficiently justified the choice of species for toxicology investigations. The monkey, mouse and rat turned out to be the most relevant species (IC_{50} of 5.07 nM, 13.9 nM and 69.8 nM respectively).

Secondary pharmacology studies revealed no off-target effects with a selectivity window of 1656-fold.

The results of safety pharmacology studies suggest that sebetralstat is not associated with adverse effects on CNS, respiratory and cardiovascular systems. However, due to narrow safety margins in animal species, the lack of sebetralstat-mediated effects on these systems cannot be fully confirmed based on non-clinical data. See clinical safety in section 2.6.8. for clinical assessment of these adverse events.

The PK/TK profile of sebetralstat was adequately investigated using validated methods. Analyses did not reveal any concerns. A large number of metabolites were observed, and some were not characterised in human excreta, but none accounted for more than 1% of the dose in urine and faeces combined. It was unclear, if all minor metabolites detected in vivo in humans in the definitive profiling and characterisation of metabolites (M30 and subsequent numbers) were detected in toxicology animal species. After clarifications provided by the applicant, it was concluded that the metabolism of sebetralstat was qualitatively similar in human and both general toxicology species.

In repeat-dose toxicity studies sebetralstat showed an intrinsic ability to induce hepatotoxicity. In NHPs, the liver was the main affected organ in 35-day daily dosing study where due to early termination of animals, exposure to sebetralstat on day 35 is unknown at 300 mg/kg/day. In addition, in 13-week daily dosing study (8382423), microscopic findings in liver were also observed which were not considered adverse by the PWG (Pathology Working Group). However, the exposure at the highest dose and NOAEL set by PWG (50 mg/kg/day) was lower (AUC values of 7390 and 6630 h*ng/mL for male and female NHPs, respectively) compared to human exposure at the maximum recommended dose (600 mg, AUC 18000 h*ng/mL). Therefore, it is possible that the doses were too low to see the exact hepatic toxic effects of the sebetralstat. Furthermore, results and conclusions from a 13-week intermittent dosing study cannot be used due to HAV infection. Finally, the remaining 26-week intermittent study (20286942) also revealed some individual hepatic effects (increased ALT and GLDH as well as microscopic findings) and, the variability of exposure data was significantly high. This variability was also observed in the study 182658, where the overall systemic exposures were over a 3-fold range between high and low values in males and almost 6-fold regarding AUC in females. All things considered, the applicant was asked to discuss if the exposure level observed in NHPs studies would cover the anticipated therapeutic concentrations in order to rule out hepatotoxicity and any effect on vital functions in humans. Based on the exposure data from the NHP studies, it was concluded that sebetralstat's pharmacokinetics adequately cover the anticipated clinical therapeutic exposure, with no evidence of hepatotoxicity or adverse effects on vital functions at the NOAEL doses and even higher exposures did not result in liver toxicity. The predicted clinical exposure is in line with these findings, and the difference in dosing regimen (intermittent vs. daily) does not change the overall safety profile. Therefore, the results of the nonclinical repeated-dose toxicity studies support the clinical use of sebetralstat in the proposed dosing regimen.

A standard battery of genotoxicity assays did not demonstrate any genotoxic potential of sebetralstat.

Regarding the 104-week carcinogenicity study, no test-item-related increase in the incidence of malignant neoplasms was noted, but sebetralstat administration was associated with some increases in benign tumours in the female livers, male pituitary and thyroid glands, testes and ovaries. These changes were considered by the applicant as common in this strain and/or a consequence of altered endocrine hormone metabolism associated with xenobiotic-induced liver enlargement and enzyme induction and, therefore not relevant to humans.

In the 26-week study in wild-type CByB6F1 Tg(HRAS) mice, a dose-related trend of bronchioloalveolar adenoma and bronchioloalveolar, adenoma/carcinoma were noted across all groups, but the incidences of these findings were within the Testing Facility historical control ranges and therefore considered to be inconsequential. Sebetralstat-related effects were considered limited to the liver (increased liver weight and minimal centrilobular hypertrophy) at 200 mg/kg/day in males and 300 mg/kg/day in females. The applicant was asked to discuss the importance of the notable higher incidence of benign thymoma in female mice treated with 100 mg/kg/day of sebetralstat and this finding was not considered attributable to sebetralstat treatment. The rationale was based on the absence of dose-response relationship and lack of statistical significance between treated groups and controls, the fact that findings from low dose and high dose groups were within Testing Facility historical control, evidence of the literature indicating thymomas as common spontaneous tumours in this mouse strain and the absence of proliferative thymic changes in other species treated with sebetralstat.

According to ICHS1, selection of high dose for carcinogenicity study should be based on a 50-fold exposure ratio (AUC) in TgrasH2 mice and 25-fold for the 2-year rat study. While the dose range chosen in the carcinogenicity studies performed can be acceptable, it cannot be excluded with absolute certainty a lack of carcinogenic potential, as the 50-fold and 25-fold exposure ratio are not met. Safety margins of 0.2 and 0.4 respectively, are obtained based on unbound AUC in males and females respectively in the 26-week study in Tg(HRAS) mice. In the 104-week rat study safety margins of 0.7 and 2.5 are obtained based on unbound AUC in males and females respectively. It should be noted that those safety margins were calculated for benign tumours formation. In the absence of significant increase in the incidence of any malignant tumours, the high dose can be used to calculate safety margins for malignant tumours formation. Safety margins of 5.7 would be obtained based on unbound AUC.

A statement regarding carcinogenicity has been implemented in SmPC in section 5.3. to reflect the lack of carcinogenicity based on a 26-week study in rasH2-Tg transgenic mice and a 104-week study in rats.

A full set of developmental and reproductive toxicity studies were performed in rats and rabbits with sebetralstat. Regarding species selection, rabbits cannot be considered as pharmacologically active species since PD data showed IC_{50} values higher than 40,000 nM regarding inhibition of rabbit plasma kallikrein enzyme (in other words, fold to human Ki was 12.3 and >6623 for rat and rabbit, respectively). However, according to ICH S5, this can still be accepted since PD effect was clearly confirmed in rats. A statement was included in SmPC in section 5.3 in relation to the fact that rabbit is not a pharmacologically relevant species.

No drug-induced effect on the fertility of male or female rats was observed, however there was an increase in preimplantation loss noted at the high dose level of 600 mg/kg/day compared to concurrent controls (1.2, 1.1, 1.0, 2.0 per litter; 8.6%, 9.8%, 7.9%, 16.2% per litter) and historical controls (range of 1.9%-13.4%; 9 studies conducted from 2015-2017). The applicant was asked to discuss further this finding. Briefly, it was explained that this was related mainly to 2 females with high preimplantation loss. In one of those females (#159), this was considered a chance finding related to mating taking place while vaginal smears taken on the morning before showed it was in oestrous phase, i.e. still sexually receptive but with poorer reproductive outcome. No cause was identified for the other female (#141), shown to be in proestrus stage before mating

and considered as an outlier. As indicated by the applicant, the HCD reflects natural variability such as timing of mating in relation to timing of ovulation. Actually, the preimplantation loss in the FEED was increased in the high dose group compared to both concurrent controls (8.6%, 9.8%, 7.9%, 16.2% at 0, 100, 300, 600 mg/kg/day, respectively) and historical controls (range of 1.9%-13.4%). In addition, the mean preimplantation loss in the subgroup of 5 control animals identified by the applicant as having oestrus smears prior to pairing was 4.5% (0-1 preimplantation loss per litter), which is lower than the mean control group value (8.6%). Both elements are not supportive of the chance finding hypothesised by the applicant as underlying the observed increase in preimplantation loss at 600 mg/kg/day. Overall, a treatment-related increase of preimplantation loss at 600 mg/kg/day cannot be excluded.

In rats, sebetralstat induced malformations (mostly cleft palate and ventricular septal defects) and embryofetal lethality. In contrast, no impact on the embryofetal development of rabbits was observed except for effects on fetal body weight and delayed ossification which may be related to effects on maternal body weight and food consumption at the high dose level. In the pre- and postnatal development study, there was no treatment-related effect on sexual maturation, neurobehavioural examinations, and reproductive performance of F1 animals exposed from implantation to weaning. The NOAEL was set at 450 mg/kg/day for both, parental females and F1 generation.

The NOAELs determined in rats for effects on fertility, embryofetal development, and pre/postnatal development were 600 mg/kg/day, 300 mg/kg/day and 450 mg/kg/day, respectively. This corresponds to unbound AUC-based safety margins of 6.9 to 8.3-fold for fertility, and of 3.0- for embryo-fetal development, respectively. In rabbits, no malformations or embryo-fetal lethality were observed at up to 6.8-fold human exposure levels based on unbound AUC. In that context, human relevance of adverse effects on rat embryofetal development cannot be excluded. According to the guideline EMEA/CHMP/203927/2005 (table 1), a label [4] (i.e. "not recommended during pregnancy in women of childbearing potential not using contraception") should be used for sebetralstat. However, considering the risk/benefit in certain circumstances, a wording stating that "*Ekterly should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus (e.g. for treatment of potentially life-threatening laryngeal attacks*)" was implemented for the pregnancy subsection of SmPC section 4.6.

Impurities can be considered as non-genotoxic impurities in accordance with ICH M7 (R2) guideline. Sebetralstat can be considered non-phototoxic. No dedicated toxicology studies are mandatory for excipients considering no novel excipients are used.

Environmental risk assessment:

PBT Assessment

According to the EMA guideline on the Environmental Risk Assessment of medicinal products for Human use, the PBT assessment shall be conducted only for compounds with a $\log K_{ow} > 4.5$ which was not the case for sebetralstat.

Screening for a specific mode of action:

The identification of a specific mode of action is a trigger for a phase II - tailored assessment. The phase I report indeed comprises an assessment of sebetralstat for its putative Endocrine disruptor property. However, no real demonstration is really presented and data supporting the conclusion are scarce in the present ERA report. However, according to mode of action, available secondary pharmacodynamics data, as well as toxicology studies assessment, this can be acceptable.

Phase I

The calculations for PECsw were run in accordance with EMA guideline. The refined PECsw value exceeded the action limit of 0.01 µg/L and a phase II study was then appropriately undertaken.

Phase II

All the studies that are recommended by EMA guidance for a phase II tier A assessment have been conducted according to OECD guidelines and under GLP. Moreover, the report on adsorption studies concluded to a limited partition to sludges. As the trigger value for Koc was not met (< 10 000 L/kg) no phase II tier B study was undertaken, in accordance with the EMA 2006 guidance.

The data summary provided by the applicant adequately reflects data in the study reports. When clearly stated in OECD guidelines, validity criteria were met. PEC / PNEC have been calculated according to EMA guideline (2006 version) for surface water, ground water, microorganisms. For the sediment compartment the PEC was derived after REACH guidance chapter R.16 (Environmental exposure assessment). As none of these PEC/PNEC ratios was above 1 (0.1 for microorganisms), no environmental risk was identified for sebetralstat when used in the treatment conditions described.

The CHMP agrees with the conclusion proposed for the groundwater and sediments compartments. For surface water and sludge compartments, some precisions should be given concerning the physical state of sebetralstat in the exposure media (see "comments on biological effects" section below). There was a discrepancy for the reported value the DT50 Total System, Parent and NER,12°C = 7946 days for the system 'Middle Pond' in the ERA and the study report. The applicant acknowledged the error and provided an amended report.

Comments on environmental fate

As sebetralstat is not readily biodegradable, its fate in a water-sediment system was studied accordingly to EMA Guideline. It was demonstrated a potential to accumulate in sediment which suggest that environmental persistence of sebetralstat in some aquatic sediment may be an issue in the long term (although sebetralstat is not to be considered for PBT assessment).

In the water-sediment system study was insufficiently considered: a 34% loss of microbial biomass was observed for the silty sediment Calwich Abbey at the end of the 100-days experiment. Whether this microbial biomass loss results from sebetralstat (or its transformation products) has not been discussed initially. The applicant clarified that the inhibitory effect of sebetralstat on the microbial biomass was investigated according to OECD 209 and 301 guidelines. and that microbial biomass in the water-sediment study was measured in untreated samples, so an inhibitory effect cannot be attributed to sebetralstat. The applicant indicated that the microbial loss observed could be due to the season at which the study was performed (early March), as a higher microbial biomass can be observed due to "Spring Flush".

In the soil and sludge adsorption study, the authors noted that sebetralstat Kd values for soils were not related to their respective OC contents. In this respect, it's unfortunate that only 3 soils were used since OECD 106 guideline indicated 5 soils should be tested, with contrasted %OC, pH and texture. That would have help to get a better understanding of the driver(s) for the adsorption of sebetralstat to solid particles. However, this observation that Kd values were not related to OC content implies that:

- The McCall classification for the mobility of chemicals in soils, based on Koc values, may lead to a questionable conclusion. Considering that sebetralstat "can be classified as having low mobility to being immobile in soils" may be somehow hypothetical.

- An uncertainty may arise in the $PEC_{sediment}$ determination. Indeed, it was calculated according to ECHA R16 guidance, using Koc to derive an adsorption coefficient to suspended solids. No alternate method is however indicated in the guidance document for deriving the $PEC_{sediment}$ value.

Comments on biological effects

Since sebetralstat has a poor aqueous solubility, the applicant was asked to confirm that organisms in algae and sludge tests were exposed only to the dissolved phase of sebetralstat. The applicant clarified that in the algae test, nominal concentrations of sebetralstat were achieved and that the tests were performed according to the OECD guidelines. Although analytical measurements are not available from the sludge study it is believed that, similarly to how the active ingredient was difficult to dissolve under laboratory conditions, it is unlikely to be fully dissolved in the environment. Therefore, no special risk is anticipated.

In addition, concerning the assessment of biological effects, it is in general required, although not always stated in validity criteria, that the assay sensitivity will be checked through the use of a reference compound of known ecotoxicity. This was reported for the algae and sludge respiration tests, but not for Daphnia magna reproduction test, chironomid test and fish test. Such positive controls are for sure routinely run by the laboratory responsible for the concerned studies, and their results should be appended to the ecotoxicity assay reports. Therefore, the applicant was asked to transmit the data concerning the positive controls that are generally run to ensure that species/strain sensitivity were in their usual range at the time when sebetralstat ecotoxicity was determined. The applicant clarified that the relevant OECD guidelines (OECD 210, OECD 211, and OECD 218) do not specifically require reference substances for sensitivity checks in chronic tests. Overall, the response is justified, but incorporating historical control data or laboratory performance benchmarks would have further supported the studies robustness.

Overall, except for the potential to accumulate in some aquatic sediments, available data suggest that sebetralstat is not expected to pose a significant risk to the environment. An error for the reported value the $DT_{50\ Total\ System,\ Parent\ and\ NER,12°C}$ for the system 'Middle Pond' in the ERA and the study report was acknowledged by the applicant, who amended the report.

Overall, except for the potential to accumulate in some aquatic sediments, available data suggest that sebetralstat is not a PBT substance and is not expected to pose a significant risk to the environment.

A corresponding statement has been put in section 5.3 of the SmPC : "Environmental risk assessment studies have shown that sebetralstat has the potential to accumulate and may persist in some aquatic sediment systems". Section 5 of the package leaflet advises: "Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment".

2.5.7. Conclusion on the non-clinical aspects

Overall, the nonclinical program supports the MAA of sebetralstat in the approved indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Trial Number/ Status/	**Trial Design**	**Main Objectives**	**Total Enrolled Sex Mean Age±SD (Range) Race**	**Trial Population**	**Dosing Regimen**	**Safety Assessments**
Healthy Subjects PK and Initial Tolerability Trials						
KVD900-101/ Completed	Phase 1, randomised, double-blind, placebo controlled, 3-part, single ascending dose trial with formulation crossover, and food effect	Safety and tolerability of 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 ± 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 × 100 mg) film-coated tablet under fed and fasted conditions Matching placebo	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, physical examinations, telemetry
KVD900-102/ Completed	Phase 1, randomised, 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 ± 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 × 100 mg film-coated tablets) given at q2h, q4h, or q8h intervals Matching placebo	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, Holter monitoring

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
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 ± 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 × 300 mg) powder in capsules	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, physical examinations
Comparative Bioavailability Trials						
KVD900-107/ Completed	Phase 1, open-label, randomised, 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 ± 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 × 300 mg) film-coated tablets that were either chewed or swallowed intact **Treatment A:** Single administration of sebetralstat 600 mg (2 × 300 mg) tablets that were chewed at Hour 0 on Day 1 **Treatment B:** Single administration of sebetralstat 600 mg (2 × 300 mg) tablets that were swallowed intact at Hour 0 on Day 1	AEs, clinical laboratory assessments, vital signs,12-lead ECGs

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
KVD900-108/ Completed	Phase 1, open-label, randomised, single-administration, 3-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 ± 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 × 300 mg) film-coated tablets, 500 mg (2 × 250 mg) ODTs, and 600 mg (2 × 300 mg) ODTs: **Treatment A:** Sebetralstat 600 mg (2 × 300 mg) ODTs at Hour 0 on Day 1 **Treatment B:** Sebetralstat 500 mg (2 × 250 mg) ODTs at Hour 0 on Day 1 **Treatment C:** Sebetralstat 600 mg (2 × 300 mg) film-coated tablets at Hour 0 on Day 1	AEs, clinical laboratory assessments, vital signs,12-lead ECGs
Drug-drug Interaction Trials						
KVD900-106/ Completed	Phase 1, 4-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 Safety and tolerability of a single administration	**Part 1:** N=17 16 males, 1 female 37.4 ± 9.20 years (21 - 52) Black or African American/white/other: 10/7/0 **Part 2:** N=16 14 males, 2 females	Healthy males and females between the ages of 19 and 55	Single administration of sebetralstat 600 mg (2 × 300 mg) film-coated tablets in the presence of index perpetrators: **Part 1:** Sebetralstat 600 mg alone (Day 1 of Period 1); itraconazole 200 mg (20 mL of 10 mg/mL) oral solution once daily for 6 days (Day 1	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, physical examinations, C-SSRS (Part 3 only)

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
		of sebetralstat alone and in combination with itraconazole (**Part 1**), eltrombopag (**Part 2**), phenytoin (**Part 3**), or quinidine (**Part 4**)	38.4 ± 10.33 years (21 - 52) Black or African American/white/other: 7/9/0 **Part 3:** N=16 12 males, 4 females 40.9 ± 8.87 years (29 - 55) Black or African American/white/Asian: 7/8/1 **Part 4:** N=16 14 males, 2 females 38.5 ± 9.73 years (24 - 55) Black or African American/white/other: 6/10/0		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 × 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 × 100 mg) capsule 3 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 2 administrations (1 × 300 mg tablet each) 1 hour prior to and 3 hours after a single	

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
					administration of sebetralstat 600 mg on Day 1 of Period 2	
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 ± 9.02 years (23 - 54) Black or African American/white/other: 2/13/1 **Part 2:** N=16 14 males, 2 females 40.9 ± 8.94 years (24 - 53) Black or African American /white/other: 2/14/0 **Part 3:** N=16 9 males, 7 females 41.3 ± 10.54 years (23 - 55) Black or African American/white/other: 1/14/1 **Part 4:** N=16 13 males, 3 females	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 600 mg (2 × 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 × 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 × 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 × 200 mg tablets), with sebetralstat 600 mg co-administered on Day 1 of Period 2	AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, C-SSRS (Parts 2 and 4 only)

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
			45.8 ± 8.21 years (28 - 54) Black or African American/white/other: 2/13/1		**<u>Part 4:</u>** Sebetralstat 600 mg alone (Day 1 of Period 1); modafinil 200 mg (1 × 200 mg) tablet for 15 days with sebetralstat 600 mg co-administered on Day 14	
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 ± 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 × 300 mg) film-coated tablets	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, physical examinations

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
KVD900-110/ Completed	Phase 1, randomised, 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 ± 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 × 300 mg), or 1,200 mg (4 × 300 mg) film-coated tablets Matching placebo	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, Holter monitoring
KVD900-109/ Completed	Phase 1, 2-part, trial Part 1: open-label Part 2: randomised, partially double-blind, placebo- and positive-controlled, 3-way crossover TQT	Part 1: to determine that the proposed supratherapeutic dose regimen of sebetralstat is safe and tolerable and achieves the targeted supratherapeutic peak plasma concentration Part 2: effect of supratherapeutic dose regimen of sebetralstat on QTcF	**Part 1:** N=8 5 males, 3 females 35.9 ± 13.82 years (20 - 54) **Part 2:** N=30 24 males, 6 females 32.6 ± 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	**Part 1:** Sebetralstat 900 mg (3 × 300 mg) film-coated tablets, every hour for 3 administrations (hours 0, 1, and 2) to total 2,700 mg **Part 2:** 3 treatments across 3 trial periods (1 treatment per period): • Treatment A: Sebetralstat 900 mg or 1,200 mg (3 × 300 mg or 4 × 300 mg, respectively) film-coated tablets; 900 mg (3 × 300 mg) given at 0 and 1 hours and 1,200 mg (4 × 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	AEs, clinical laboratory assessments, vital signs, 12-lead ECGs

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
Phase 2 - 3 Trials in Patients with HAE type 1 or 2						
KVD900-201/ Completed	Phase 2, two-part, two-sequence, two-period crossover Part 1: open label Part 2: randomised, double-blind, placebo-controlled	Efficacy of sebetralstat compared to placebo in halting the progression of a peripheral or abdominal attack of HAE Safety and tolerability of sebetralstat PK profile of sebetralstat when taken during the intercritical period between HAE attacks PD profile of sebetralstat in reducing the concentration of residual cleaved HK during the intercritical period between HAE attacks PD profile of sebetralstat in reducing activated plasma enzyme activity during the intercritical period between HAE attacks	Total dosed: N=68 31 males, 37 females 38.3 ± 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 1 or 2	**Part 1:** Open-label sebetralstat 600 mg (6 × 100 mg) film-coated tablets **Part 2:** Sebetralstat 600 mg (6 × 100 mg) film-coated tablets Matching placebo	AEs, clinical laboratory assessments, vital signs,12-lead ECGs, physical examinations

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
KVD900-301/ Completed	Phase 3, double-blind, randomised, placebo-controlled, crossover, multicentre trial	Clinical efficacy, safety, and tolerability of sebetralstat compared with placebo for the on-demand treatment of HAE attacks	Total dosed: N=110 44 males, 66 females 37.7 ± 14.96 years (13 - 74) Black or African American/white/Asian/other/ not reported: 1/92/10/1/6	Male and female patients 12 years of age and older with a confirmed diagnosis of HAE type 1 or 2	Up to 2 administrations of blinded IMP administered at least 3 hours apart Sebetralstat 300 mg (1 x 300 mg) tablet plus 1 placebo tablet, 600 mg (2 x 300 mg) tablets, or 2 matching placebo tablets in response to each qualifying attack of HAE If needed (as determined by the patient), an additional administration of IMP (of the same assigned treatment) may have been administered for each attack at least 3 hours after the first administration	AEs, clinical laboratory assessments, vital signs,12-lead ECGs

Trial Number/ Status/	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
KVD900-302/ Ongoing (interim data as of data cutoff date of 15 Jan 2024)	Phase 3, open-label multicentre, long-term safety trial	Safety of long-term administration of sebetralstat; long-term efficacy of sebetralstat; safety and efficacy of sebetralstat when used as short-term prophylaxis	Total dosed: N=84 30 males, 54 females 35.9 ± 15.49 years (13 - 77) Black or African American/white/Asian/other/ not reported: 0/63/12/2/7	Male and female patients 12 years of age and older with a confirmed diagnosis of HAE type 1 or 2 Includes patients who were randomised in KVD900-201, patients who were randomised in KVD900-301, and patients who did not participate in either trial	Single administration of sebetralstat 600 mg (2 x 300 mg) tablets to treat each HAE attack. If needed (as determined by the patient), an additional IMP administration may be administered for each attack at least 3 hours after the first administration Patients may also use sebetralstat as a short-term prophylactic therapy prior to undergoing surgical, dental, or medical procedures: 3 administrations of sebetralstat are taken as short-term prophylaxis, with each administration approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure	AEs, clinical laboratory assessments, vital signs,12-lead ECGs

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Sebetralstat has been studied at doses ranging from 5 mg to 1,200 mg (maximum total daily dose 3,000 mg) in two Phase 1.

- Clinical pharmacology characterisation of sebetralstat has been investigated in ten dedicated studies in healthy volunteers, together with studies conducted in patients with HAE type 1 or 2, including one Phase 2 trial (KVD900-201) and an elective Phase 3 PK subtrial in paediatric patients aged 12 to <18 years old (KVD900-302a) have been submitted. Furthermore, the data from clinical trials were used to develop population PK (PopPK) model and two physiologically based pharmacokinetic (PBPK) models. PBPK models were developed to waive clinical trials in patients with severe hepatic impairment and to investigate the impact of stomach pH on PK of sebetralstat.
- Bioanalytical Methods:
    - Three methods were used in order to analyse sebetralstat concentrations in clinical studies, namely YDS/072, YDS/090, YDS/103, and their accompanying long-term stability studies YDS/073, YDS/133, and YDS/118. Two validated bioanalytical methods (YDS/072 and YDS/090) were used during clinical development to quantify sebetralstat in human plasma by a LC-MS/MS technique. One validated method (YDS/103) was used during clinical development to quantify sebetralstat in dried human blood using Mitra® tips and using liquid extraction followed by LC-MS/MS, to help facilitate the collection of samples in adolescents and paediatric patients.
    - The applicant has assumed a 1:1 conversion factor for sebetralstat concentration from blood to plasma, despite the submitted documentation indicating a mean blood-to-plasma (B/P) ratio of 0.8.
    - Pharmacodynamics of sebetralstat was investigated in studies KVD900-101, KVD900-102, KVD900-110 and KVD900-201 by assessing the enzyme activity of plasma activated kallikrein (PKa) using ex-vivo assays after triggering of its activation The assays allowed to determine in diluted plasma of dosed subjects by sebetralstat the inhibition of the PKa activity in comparison with PKa activity in the (diluted) plasma of same subjects before dosing of sebetralstat (pre-dose samples).
- NCA approach was used for the estimation of pharmacokinetic variables (e.g. AUC, C_{max}, C_{trough}, T_{max}, $t_{½}$ and Cl/F) for formal (rich sampling) PK studies. Additionally, two population PK (PPK) and two Physiologically-Based-PK (PB-PK) analyses were performed.
- PPK:
    - A population pharmacokinetic analysis was carried out to describe the absorption, distribution and elimination of sebetralstat and the covariates influencing it. Oral absorption was described by a mixed first-order and zero-order process with an absorption lag time on the zero-order process. Elimination was described by a two-compartment first order elimination. Many potential covariates were tested and included in the final model.

All parameters were estimated with high precision as RSD% was below 30%. Shrinkage was relatively low for all parameters. Goodness-of-fit plots of the final model for sebetralstat against the population model prediction and individual model prediction showing a normal random scatter around the identity line and indicated the absence of significant bias. The pcVPC demonstrates that the final model adequately described the time course of sebetralstat plasma concentrations and its associated variability after oral administration.

- The PPK model previously developed is updated by inclusion of the newly generated data in adolescent (n=6) and paediatric subjects (n= 14). Following the inclusion of the data, the PPK model parameter estimates were already similar to the previously developed PPK model.

- PK-PD:

  The enzyme activity of Kallikrein was collected was measured in healthy volunteers and patients in clinical studies: KVD900-101, KVD900-102, KVD900-110, and KVD900-201. A PPK-PD model was developed using this PD marker. The enzyme activity base PPK-PD model was a direct effect inhibitory model with a maximum inhibitory effect (I_{max}) function with Hill factor (gamma).

- PBPK:

  A PB-PK model was developed in order to describe the PK of sebetralstat and to predict the systemic exposure in subjects with severe hepatic impairment and waive a clinical study in subjects with severe hepatic impairment.

- After oral administration sebetralstat is rapidly **absorbed** with C_{max} reached within 1 to 2 hours approximately. Plasma concentrations declined in biphasic manner, reflecting rapid distribution of the drug followed by a slower elimination phase. The **elimination** half-life at the 300 mg therapeutic dose is approximately 5 hours

- No information regarding the absolute bioavailability could be made as no PK investigation of sebetralstat by IV route has been performed. The absence of such investigation is explained by the poor solubility of the drug substance.

- The minimal the absorbed dose fraction made from the finding of mass-balance study is approximately 75%. However no reliable estimation of the absolute bioavailability could be made.

- Different formulations were used through the clinical development program: powder in capsules, 100 mg uncoated tablets, 100 mg coated tablets, 300 mg white coated tablets and yellow coated tablet. This later formulation is intended for marketing. In the response documentation, the applicant provides a synthetic and comprehensive presentation of the formulations used in the clinical program. This allows a comprehensive oversight on the comparability of these formulations and the identification of the need of bridging investigations. Based on the outcome of the provided dissolution tests, the data collected with different formulations could be bridged.

- **Food effect**: Based on the investigation of the early 100 mg tablet (Study KVD900-101), the absorbed fraction of sebetralstat in marginally enhanced but the rate of absorption (C_{max} and T_{max}) significantly reduced when the drug is administered with food. Sebetralstat exhibits extensive **distribution** to peripheral tissue. No estimation of the absolute Vd is available. The apparent Vd/F is ranging between 200 to 500 L upon studies. The binding to plasma circulating proteins is moderate 77% and no accumulation in blood cells is observed. In the final PopPK model the central volume of

distribution was estimated to be 70 L, while the peripheral volume of distribution was estimated to be 37.7 L. The apparent volume of distribution estimated using NCA approach is 208 L after a 300 mg dose.

- Based on the outcome of mass-balance study, the overall mean recovery of radioactivity in urine and feces was 95.8% over the 216-hour study, with observed mean recovery of total radioactivity in urine and feces of 32.4% and 63.4%, respectively. Most of the administered radioactivity was recovered in the first 96 hours postdose (mean of 90.2%). Unchanged sebetralstat accounted for a mean of 8.66% of the radioactivity excreted in the urine through 48 hours and for a mean of 12.5 % in feces up to 144 h post-dose.
- After oral administration, plasma concentrations of sebetralstat decline in a biphasic manner. The estimation of terminal elimination half-life varies upon studies between 3 and 6 hours. The geometric mean apparent clearance (CL/F) was 38.5 L/h. Metabolism appears to be the major elimination pathway.
- An attempt to elucidate the **metabolism** pathway is made by the applicant based on *in vitro* investigations on human materiel and metabolite profiling in plasma, urine and faeces, performed in the mass-balance study. *In vitro* study using human material and DDI studies shows that CYP3A4 plays a major role in the metabolism of sebetralstat. The plasma, urine and feces metabolites profiling identified numerous metabolites (40) suggesting that the metabolism of sebetralstat is complex. No circulating major metabolite (exceeding 10 % the exposure to the parent drug or the total radioactivity) was identified. Even few information regarding the potential for accumulation of quantifiable metabolites is available, this is not considered of concern. Sebetralstat is not intended for repeated use. A comprehensive presentation of the metabolism and excretion routes including the enzymes and mechanisms involved is provided.
- No active metabolite with a large contribution to activity is identified there no specific characterisation of metabolites was performed.
- CYP3A4 is the major enzyme responsible for sebetralstat metabolism as suggested by *in vitro* studies. No polymorphically expressed enzymes such as CYP2D6, CYP2C19, N-acetyl transferase are significantly involved in the metabolism.
- **Dose proportionality** was statistically evaluated in studies KVD900-101 and KVD900-110. C_{max} is proportional to dose across the dose range (5 to 300 mg). For higher dose (600 mg), the observed C_{max} is markedly less than proportional.
- Overall exposure (AUC) evolves roughly proportionally for doses up to 300 mg. For higher doses (600 mg), a clear trend toward less proportionality is observed. Overall, the data suggest a saturable absorption of sebetralstat for doses exceeding 300 mg. However, considering the limited size of the study (n=6) this statement should be sought cautiously.
- No information are available regarding time dependency. 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.
- Sebetralstat, exhibits moderate inter-subject variability (30-40%) and low to moderate intra-subject variability (18-30%).
- PK profiles are almost similar in healthy volunteers and patients with HAE.

- No dedicated investigation was performed in subjects with renal impairment.
- A formal PK investigation has been performed in subjects with mild and moderate HI. Systemic exposure is marginally higher in subjects with mild HI. Hence, it is agreed that no dose adjustment is necessary in this group of subjects.

  However, much higher systemic exposure (+63% for C_{max} and +100 % for AUC) is observed in subjects with moderate HI. While the magnitude of such increase of systemic exposure might have some clinical impact, given that the safety data in this sub-group are too limited to be reassuring, it is agreed as being mitigated by the one shot treatment with short treatment duration and the fact that no PK accumulation is expected in cases of repeated use given the short half-life. Finally, no additional warning is required beside that related to the risk of QT prolongation in case of cumulative risk factors (e.g., moderate hepatic impairment and co-administration of strong CYP3A4 inhibitors).
- No dedicated study was performed in subject with severe HI. The prediction made by the PBPK modelling of the systemic exposure in severe HI could not be endorsed, as prediction power of the model is questionable. As an illustration, significant higher exposure was predicted in mild HI subjects by the model (respectively 1.27 and 1.77-fold increase for C_{max} and $AUC_{0\text{-}inf}$). This not confirmed by the outcome of the formal PK study KVD900-104.
- Although no dedicated formal PK study was conducted to compare PK in male and female subjects, a separate analysis of gender completed with PK data from KVD900-201 and relevant phase 1 studies (KVD900-106, KVD900-107, KVD900-108, KVD900-110, and KVD900-112 shows no clear gender effect and confirms the findings of the PPK that assigns any differences in PK exposure observed between sexes as effects of relative body weights on clearance and volumes of distribution.
- The data collected in white Caucasian, Japanese and Chinese subjects doesn't reveal any noticeable difference in systemic exposure to sebetralstat at the three dose levels tested: 300- 600 & 1200 mg. However, no formal dedicated studies were conducted in black Africans/Americans, Indians. Race as covariate have been tested in popPK model. Although Asian race was retained in the final model as significant covariate, however PK parameters AUC and C_{max} were 16% higher and 10% lower, respectively.
- No dedicated study was performed in underweighted or obese patients. No specific investigation of the effect of body weight on the PK of sebetralstat has been performed. The effect of body weight (allometric scale) on CL/F, Q/F, V2/F and V3/F was included as a covariate in the proposed PPK final model. A stratified comparison of plasma exposures by BMI is presented by the applicant. This included data collected in 117 overweighed subject and 55 obese subjects. Geometric mean plasma exposures were comparable in overweighed, obese subjects and normal weight subjects.
- Elderly: No dedicated PK investigation was performed in elderly subjects.

Special populations

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Sebetralstat Phase 1 trials	4/457	0/457	0/457
Sebetralstat Phase 2/3 trials	6*/254	1/254	0/254

***** *one patient was enrolled in KVD900-201 where plasma samples were collected and PK parameters were assessed*

- **Paediatric patients:**

  The PPK model previously developed is updated by inclusion of the newly generated data in adolescent (n=6) and paediatric subjects (n= 14).

Pharmacokinetic interaction studies

As an object

The *in vitro* data indicated that sebetralstat is primarily metabolised by CYP3A4 and is a substrate of P-gp and BCRP. The DDI risks between sebetralstat and modulators of CYP3A4, P-gp, and BCRP were assessed in two clinical studies (KVD900-106 and KVD900-112).

In study KVD900-106, sebetralstat was confirmed as a sensitive CYP3A4 substrate. Co-administration with the CYP3A4 inhibitor itraconazole (Strong CYP3A4/P-gp Inhibitor) led to a >5-fold increase in AUC and a 135% rise in C_{max} ($AUC_{0\text{-}inf}$ 90% CI: 456%-594%; C_{max} 90% CI: 193%-287%). Conversely, the CYP3A4 inducer phenytoin reduced AUC by 83% and C_{max} by 66% ($AUC_{0\text{-}inf}$ 90% CI: 14.4%-20.7%; C_{max} 90% CI: 24.5%-46.2%). P-gp inhibition by quinidine had a minimal effect, increasing AUC by 14% and C_{max} by 18% ($AUC_{0\text{-}inf}$ 90% CI: 97.1%-134%; C_{max} 90% CI: 88.2%-157%), confirming that CYP3A4 inhibition was the primary driver of interactions. Co-administration with eltrombopag (BCRP Inhibitor) showed a similar $AUC_{0\text{-}inf}$, with 90% CIs for the GMR within the 80%-125% range, while C_{max} increased by 12% (90% CI: 86.0%-145%), suggesting weak BCRP inhibition.

In study KVD900-112, co-administration with verapamil (a moderate CYP3A4 inhibitor) increased $AUC_{0\text{-}inf}$ by 102% and C_{max} by 76% (90% CI for $AUC_{0\text{-}inf}$: 183%-224%, C_{max}: 147%-212%). Efavirenz (a moderate CYP3A4 inducer) decreased $AUC_{0\text{-}inf}$ by 79% and C_{max} by 63% ($AUC_{0\text{-}inf}$ 90% CI: 17%-26%, C_{max} 90% CI: 28%-48%), suggesting moderate to strong CYP3A4 induction. Cimetidine (a weak CYP3A4 inhibitor) lowered $AUC_{0\text{-}inf}$ by 12% and C_{max} by 22% ($AUC_{0\text{-}inf}$ 90% CI: 73%-105%, C_{max} 90% CI: 63%-96%) and Modafinil (a weak CYP3A4 inducer) reduced $AUC_{0\text{-}inf}$ by 21% and C_{max} by 11% ($AUC_{0\text{-}inf}$ 90% CI: 65%-95%, C_{max} 90% CI: 64%-124%), these suggest a weak inhibition and induction.

In the simulation report (Report KVD900-PPK1_SIM1), a dosing scenario of 900 mg (3x300 mg) at 0 hours was simulated. The resulting C_{max} values were as follows: Mean (CV%) = 8580 (53.8%) ng/mL, Median (min, max) = 7600 ng/mL (1470, 38100), and Geometric Mean (Geo.CV%) = 7490 (57.1%) ng/mL. Although some patients that are concomitantly taking an inducer drug may require a higher sebetralstat dose of 900 mg to achieve therapeutic blood concentrations, the simulation data clearly indicated that certain individuals can reach very high plasma levels (with a maximum of value of 38100 ng/mL). This could potentially impact the QT interval, as the concentration-QTc analysis showed that the upper bound of the two-sided 90% CI remains below 10 msec at concentrations lower than 16900 ng/mL.

As a precipitant

The potential of sebetralstat to act as a precipitant of the several CYPs enzymes and transporters was assessed *in vitro* (see section below for details).

Pharmacokinetics using human biomaterials

The potential of sebetralstat to act as a direct or time-dependent inhibitor (TDI) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, as well as various UGT enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7), was evaluated in the vitro studies CYP0603_R7 and 182574. A concentration-dependent direct inhibition of CYP3A4 was observed, with IC_{50} values of 120 µM and 121 µM for testosterone and midazolam metabolism, respectively. Additionally, a concentration-dependent inhibition of CYP2C9 was noted, with an IC_{50} of 30.1 µM. The results demonstrate inhibition of UGT1A1, UGT1A3, UGT1A4, and UGT1A9, with IC_{50} values of 87.9, 90.1, 57.5, and 31.3 µM, respectively. No or minimal direct inhibition and TDI was observed for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6, with IC_{50} values exceeding 200 µM.

The potential for sebetralstat to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 was assessed in an *in vitro* study (Study 181759) using plated human hepatocytes from three donors. The results showed that sebetralstat induced all tested CYP enzymes at the highest concentration (100 µM) but not at concentrations below 10 µM, except for CYP3A4, which exhibited a 1.8- to 5.6-fold induction at 10 µM compared to vehicle controls.

A study was performed to assess whether sebetralstat is an inhibitor *in vitro* of the SLC transporters OAT1, OAT3, OCT2, MATE1, MATE2- K, OATP1B1 and OATP1B3, and whether it is a time-dependent inhibitor of OATP1B1 and OATP1B3 (Study KVS/REP/20). The potential of sebetralstat (at concentrations up to 100 µM) to inhibit transporters was studied in MDCK cells singly transfected with MATE2-K (and control MDCK cells) or human embryonic kidney 293 cells (HEK293) cells singly expressing all other studied transporters (and control HEK293 cells). The results indicated no inhibition of P-gp and OAT1 over the tested concentration range (0.1-100 µM), with IC_{50} values exceeding 100 µM. Moderate inhibition was observed for OATP1B1 and OATP1B3, with IC_{50} values of 95.4 µM and 60.1 µM, respectively, and no significant change following pre-incubation, indicating no time-dependent inhibition. Sebetralstat inhibited OAT3, OCT2, MATE1, MATE2-K, and BCRP, with IC_{50} values of 19.2 µM, 5.28 µM, 8.05 µM, 7.76 µM, and 82.3 µM, respectively.

2.6.2.2. Pharmacodynamics

Mechanism of action

Sebetralstat (KVD900) is a novel small molecule inhibitor of human plasma kallikrein (PKa). HAE is characterised by recurrent episodes of increased vascular permeability and oedema mediated by bradykinin (BK) generated through the activity of PKa. At the initiation of an HAE attack, Factor XII (FXII) is activated to Factor XIIa (FXIIa), which in turn generates PKa through cleavage of plasma prekallikrein. PKa cleaves high-molecular weight kininogen (HK) to generate BK and further activates FXIIa, thus amplifying kallikrein-kinin system (KKS) activation and the generation of more BK. Inhibition of PKa by sebetralstat was shown to both suppress cleavage of HK and generation of FXIIa. These data show that sebetralstat, through inhibition of PKa, reduces the generation of BK and suppresses amplification of upstream KKS activity, thereby halting the progression of HAE attacks.

Primary and Secondary pharmacology

Primary pharmacology

In phase I study KVD900-101, the pharmacological activity of sebetralstat was determined using two different exploratory assays: one to determine inhibition of PKa enzyme activity and one to determine inhibition of PKa cleavage of endogenous HK to cleaved HK (cHK). The measurement of cHK is often used as a surrogate marker for BK, which is the mediator of the swelling in HAE attacks, as BK has a very short half-life of 60 seconds.

At sebetralstat dose levels of 300 mg and 600 mg, geometric mean inhibition of PKa activity in the plasma was maintained above 95% for at least 3 to 4 hours. Administration of 160 mg resulted in geometric mean inhibition of approximately 90% by 2 hours and less than 80% by 4 hours. The profile of inhibition of enzyme activity was unaffected by the formulation of sebetralstat (formulated tablet or powder in capsule). No clinically significant food effect was observed on the mean PD profile of sebetralstat 600 mg provided in fed and fasted state. Mean PKa inhibition of >90% was achieved by 30 minutes in both states.

In study KVD900-102, the objective was to determine the inhibitory capability of multiple oral administrations of sebetralstat in subject plasma, when administered at different dose intervals. Plasma from all subjects was evaluated for enzyme activity using an ex vivo dextran sulphate (DXS)-activated plasma assay. PKa enzyme activity was measured in both pre-dose and post-dose plasma to determine the inhibitory effect of sebetralstat on activated PKa enzyme activity after oral dosing. In all cohorts, the first sebetralstat administration achieved rapid and near complete inhibition of DXS-activated PKa activity in plasma. Mean maximal inhibition of PKa activity was >98% across all cohorts.

Study KVD900-110 assessed the profile of sebetralstat inhibition of PKa enzyme activity in three ethnicities. Overall, the PD profiles matched the PK profiles and were similar to those seen in KVD900-101 and KVD900-102.

In study 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). The 600 mg dose level of sebetralstat rapidly led to inhibition of HK cleavage in the activated plasma samples. In pre-dose samples, PKa enzyme activation with DXS induced near complete depletion of HK, with corresponding increase in the appearance of cHK. Plasma samples obtained from 15 minutes up to 4 hours post-sebetralstat dose were all protected from DXS-stimulated activation of PKa, depletion of HK, and displayed cHK levels were comparable with un-activated plasma.

Secondary pharmacology

The applicant provided cardiac monitoring results, which are discussed in the section on Clinical Safety.

2.6.3. Discussion on clinical pharmacology

Sebetralstat has been studied at doses ranging from 5 mg to 1,200 mg (maximum total daily dose 3,000 mg) in two Phase 1. Clinical pharmacology characterisation of sebetralstat has been investigated in ten dedicated studies in healthy volunteers, together with studies conducted in patients with HAE type 1 or 2, including one Phase 2 trial (KVD900-201) and an elective Phase 3 PK subtrial in paediatric patients aged 12 to <18 years old (KVD900-302a) have been submitted. Furthermore, the data from clinical trials were used to develop population PK (PopPK) model and two physiologically based pharmacokinetic (PBPK) models. PBPK models

were developed to waive clinical trials in patients with severe hepatic impairment and to investigate the impact of stomach pH on PK of sebetralstat.

Bioanalytical Methods

The applicant has assumed a 1:1 conversion factor for sebetralstat concentration from blood to plasma, despite the submitted documentation indicating a mean blood-to-plasma (B/P) ratio of 0.8. While this assumption was not scientifically justified the impact on the overall study results is considered minimal

NCA approach was used for the estimation of pharmacokinetic variables (e.g. AUC, C_{max}, C_{trough}, T_{max}, t½ and Cl/F) for formal (rich sampling) PK studies. Additionally, two population PK (PPK) and two Physiologically-Based-PK (PB-PK) analyses were performed.

PPK

Oral absorption was described by a mixed first-order and zero-order process with an absorption lag time on the zero-order process. Elimination was described by a two-compartment first order elimination. Many potential covariates were tested and included in the final model.

Given the complexity of the final model (around 20 parameters), its plausibility could be questioned. Therefore, any conclusion made on the basis of the model should be handled cautiously and considered only of supportive value.

The PPK model previously developed has been updated by inclusion of the newly generated data in adolescent (n=6) and paediatric subjects (n= 14). Following the inclusion of the data, the PPK model parameter estimates were already similar to the previously developed PPK model.

PK-PD

The enzyme activity of Kallikrein was collected was measured in healthy volunteers and patients in clinical studies. While the model is predictive and supportive of the plasma kallikrein inhibition observed in clinical trials, it is unknown what level of inhibition is needed to drive efficacy and if that is consistent from patient to patient and attack to attack. Therefore, this information is only supportive.

PBPK

A PB-PK model was developed in order to describe the PK of sebetralstat and to predict the systemic exposure in subjects with severe hepatic impairment and waive a clinical study in subjects with severe hepatic impairment. The predictive performances of the model in subjects with hepatic impairment (HI) is poor as shown by the ratio Observed/predicted $AUC_{0\text{-}inf}$ in mild HI subjects. It can be acknowledged that the misspecification could be linked to the paucity of the available data. However, no firm assertion could be made.

Different formulations were used through the clinical development program: powder in capsules, 100 mg uncoated tablets, 100 mg coated tablets, 300 mg white coated tablets and yellow coated tablet. Based on the outcome of the provided dissolution tests, the data collected with different formulations could be bridged.

Food effect

Based on the investigation of the early 100 mg tablet (Study KVD900-101), the absorbed fraction of sebetralstat in marginally enhanced but the rate of absorption (C_{max} and T_{max}) significantly reduced when the drug is administered with food. The effect of food on the absorbed fraction is deemed to not clinically significant. However, the magnitude of the increase in the rate of absorption could plausibly impact the onset

of the effect. Considering the nature of the indication, a rapid onset of the effect is to be pursued. The SmPC describes in section 5.2 the food impact. However, it is agreed that the drug can be given regardless of food in SmPC in section 4.2.

An attempt to elucidate the metabolism pathway is made by the applicant based on in vitro investigations on human materiel and metabolite profiling in plasma, urine and faeces, performed in the mass-balance study. Even few information regarding the potential for accumulation of quantifiable metabolites is available, this is not considered of concern. Sebetralstat is not intended for repeated use.

CYP3A4 is the major enzyme responsible for sebetralstat metabolism as suggested by in vitro studies.

Dose proportionality

Overall exposure (AUC) evolves roughly proportionally for doses up to 300 mg. For higher doses (600 mg), a clear trend toward less proportionality is observed. Overall, the data suggest a saturable absorption of sebetralstat for doses exceeding 300 mg. However, considering the limited size of the study (n=6) this statement should be sought cautiously.

Sebetralstat, exhibits moderate inter-subject variability (30-40) and low to moderate intra-subject variability (18-30%).

No dedicated investigation was performed in subjects with renal impairment. However, according to the posology proposed, i.e. maximum of two doses of 600 mg administered 3 hours apart, it is very unlikely that the PK could be influenced by renal impairment. No dose adjustment in required in the SmPC.

A formal PK investigation has been performed in subjects with mild and moderate HI. Systemic exposure is marginally higher in subjects with mild HI. Hence, it is agreed that no dose adjustment is necessary in this group of subjects.

However, much higher systemic exposure (+63% for C_{max} and +100 % for AUC) is observed in subjects with moderate HI. While the magnitude of such increase of systemic exposure might have some clinical impact, given that the safety data in this sub-group are too limited to be reassuring, it is agreed as being mitigated by the one shot treatment with short treatment duration and the fact that no PK accumulation is expected in cases of repeated use given the short half-life. Finally, no additional warning is required besides that related to the risk of QT prolongation in case of cumulative risk factors (such as combination of moderate hepatic impairment and co-administration of strong CYP3A4 inhibitors).

No dedicated study was performed in subject with severe HI. Sebetralstat is not recommended in those patients as reflected in section 4.2 of the SmPC.

Based on data available, no specific recommendations or dose adjustment is necessary with regard to BMI status, gender or race. However, no reliable estimation of the systemic exposure in underweighted subjects could be made as no subject underweighted was enrolled in the clinical trials.

Elderly patients

No dedicated PK investigation was performed in elderly subjects. Very limited number of elderly subjects were included in the clinical trials, but no dose adjustment is required.

Paediatric patients

Based on the refined model, the systemic exposure was simulated at the two dose levels 300 and 600 mg and compared to that actually observed in the adolescent group (n=6 treated with 600 mg dose) and adult

patients. The reported data indicates that systemic exposure in adolescent (even slightly higher) is comparable to that observed and simulated at the 600 mg dose to that observed in adult patients. However, the simulated exposure at the claimed 300 mg is noticeably higher in adolescent patients (155 %). No PK data is collected in adolescent patients treated with the 300 mg dose. However, the available PK data with the 600 mg dose in conjunction with the outcome of clinical trials (KVD900-301 and KVD900-302) preclude a significant safety issue in this subgroup of patients. Thus, no dose adjustment appears to be necessary in adolescent patients.

PK interactions

Sebetralstat as an object drug

The in-vitro data showed that CYP3A4 was responsible for the majority of sebetralstat metabolism, with a minor contribution from CYP2C8. Additionally, sebetralstat is a substrate of P-gp, and BCRP. Hence the DDI risk with this enzyme and transporters modulators could not be ruled out. Therefore, the amplitude of the interactions with CYP3A4, P-gp, and BCRP modulators were assessed in two clinical studies (KVD900-106 and KVD900-112).

Based on results of these studies, the applicant concludes that no dose adjustment is required when sebetralstat is co-administered with CYP3A4 inhibitors or weak inducers. This conclusion appears acceptable, as the significant increases in C_{max} and AUC of sebetralstat (600 mg) following co-administration with itraconazole did not negatively impact safety. The safety profile remained comparable to that observed with itraconazole alone, with a total of 21 treatment-emergent adverse events (TEAEs) reported by 8 participants (47%). Specifically, 3 participants (18%) experienced TEAEs following sebetralstat administration alone, 5 participants (29%) following itraconazole alone, and 5 participants (31%) following the combination of itraconazole and sebetralstat.

As moderate and strong CYP3A4 inducers significantly decreased sebetralstat plasma concentrations, the applicant proposed a dose increase to 900 mg in the case of concomitant use with a strong or moderate CYP3A4 inducer. Therefore, a wording in section 4.2 of the SmPC regarding the use of a 900 mg dose of sebetralstat in combination with CYP3A4 inducers has been added.

During the review process, the applicant was asked to discuss the extent of DDI risk when sebetralstat is co-administered with CYP3A4 modulators in populations with varying degrees of hepatic impairment. They concluded that no dose adjustment is needed for CYP3A4 inhibitors or inducers in subjects with mild hepatic impairment or for CYP3A4 inducers in subjects with moderate HI which was agreed. It was also agreed for patients cumulating both moderate hepatic impairment and are taking a strong CYP3A4 inhibitor, that dose adjustment consisting of a single 300 mg dose was to be recommended.

Additionally, since sebetralstat solubility is high in low pH media and simulated gastric fluid and low in higher pH media and simulated intestinal fluids, for the purposes of BCS classification sebetralstat has low solubility and is classified as a BCS class IV drug. In cases where pH modifications could impact drug bioavailability, a dedicated in vivo DDI study investigating the effect of drugs which increase gastric pH on sebetralstat exposure is requested in line with the Interaction Guideline (CPMP/EWP/560/95/Rev. 1 Corr. 2**), since the absence of such an effect has not been sufficiently justified by the PBPK model. A study with multiple-dose treatment with a PPI is recommended, as this is generally considered to give the worst-case effect on gastric pH. The applicant provided additional analyses suggesting that PPI use does not significantly affect sebetralstat absorption. However, these conclusions are limited by the lack of validation of the PBPK model used, especially given its prior overprediction in hepatic impairment. The clinical data are also insufficient due to uncertainties around ARA use timing, adherence, and small sample size. As such, the current evidence is

not adequate to rule out a clinically relevant interaction and a dedicated DDI study or stricter SmPC wording in section 4.5 has been required was agreed by the applicant.

Sebetralstat as a precipitant drug

The potential of sebetralstat to act as a direct or time-dependent inhibitor (TDI) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, as well as various UGT enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7), was evaluated in study CYP0603_R7. However, the study design was inadequate for assessing the CYP inhibition potential. The tested concentration range (0.1 to 25 µM) did not encompass the worst-case scenarios expected at both systemic levels (50*Cmax,u, equivalent to 72.24 µM) and intestinal levels (0.1 × dose/250 ml, i.e., 244.14 µM). Therefore, the results for CYP inhibition were inconclusive.

In contrast, the study setup for assessing UGT inhibition was more appropriate, utilizing suitable systems, control substrates, and inhibitors. Although the concentration range (0.1 to 100 µM) did not fully cover the worst-case scenario at systemic levels (50*Cmax,u, i.e., 72.24 µM), it was sufficient to demonstrate inhibition of UGT1A1, UGT1A3, UGT1A4, and UGT1A9, with IC_{50} values of 87.9, 90.1, 57.5, and 31.3 µM, respectively. Consequently, a potential clinical DDI risk with substrates of UGT1A4, and UGT1A9 enzymes cannot be ruled out and has been reflected in section 4.5 of the SmPC, given that there IC_{50} fall below the ICH M12 cut-off of 50× Cmax,ss, unbound (i.e. 72.2 µM). Sebetralstat is not considered an inhibitor of UGT1A6 or UGT2B7, as IC_{50} values exceeded 100 µM.

The potential of sebetralstat to act as a direct inhibitor or TDI of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was reassessed in study 182574. This time, the study design was appropriate, utilizing an adequate system along with proper control substrates and inhibitors. The concentration range tested (0.1 to 200 µM) covered the worst-case scenario at systemic levels (i.e., 72.24 µM), although it did not fully cover the expected intestinal levels (i.e., 244.14 µM). However, this may be sufficient given the low solubility of sebetralstat.

The results demonstrated either no or minimal direct inhibition and TDI for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6, with IC_{50} values exceeding 200 µM. Based on these findings, the potential for clinical DDI with substrates of these CYP enzymes can be excluded. A concentration-dependent direct inhibition of CYP3A4 was observed, with IC_{50} values of 120 µM and 121 µM for testosterone and midazolam metabolism, respectively. The DDI risk could be ruled out taking into account the limited intestinal solubility.

However, a concentration-dependent inhibition of CYP2C9 was noted, with an IC_{50} of 30.1 µM. Consequently, a potential clinical DDI risk with CYP2C9 substrates cannot be ruled out even with the intermittent use of sebetralstat, given that there IC_{50} fall below the ICH M12 cut-off of 50× Cmax,ss, unbound (i.e. 72.2 µM). These risks were asked to be highlighted in the SmPC (section 4.5 and 5.2), along with appropriate recommendations or precautions to be considered in clinical practice, such as considering the interval between administrations. In response, the applicant has discussed that it was not feasible to resolve the DDI issue by considering interval administration. Therefore, a recommendation that that co-administration with NTI substrates of the affected enzymes should be avoided unless clinically warranted has been added in the SmPC in section 4.5. While routine therapeutic monitoring cannot be foreseen given the short treatment duration, it is important that prescribers are clearly informed of the potential risk.

The potential of sebetralstat to inhibit ABC transporters (P-gp, BCRP, and BSEP) and SLC transporters (OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3), as well as its potential time-dependent inhibition of OATP1B1 and OATP1B3, was assessed in vitro (Studies KVS/REP/22 and KVS/REP/20). The experimental design of these studies appears acceptable, employing an appropriate system with relevant control substrates

and inhibitors. The concentration range tested (0.1 µM to 100 µM) almost covers the highest anticipated both systemic and hepatic concentrations but not intestinal concentration. However, given the low solubility of sebetralstat and the provided results, this is considered sufficient.

The results indicated no inhibition of P-gp and OAT1 over the tested concentration range (0.1-100 µM), with IC_{50} values exceeding 100 µM. Moderate inhibition was observed for OATP1B1 and OATP1B3, with IC_{50} values of 95.4 µM and 60.1 µM, respectively, and no significant change following pre-incubation, indicating no time-dependent inhibition. Sebetralstat inhibited OAT3, OCT2, MATE1, MATE2-K, and BCRP, with IC_{50} values of 19.2 µM, 5.28 µM, 8.05 µM, 7.76 µM, and 82.3 µM, respectively.

In vitro studies showed that sebetralstat exhibits an inhibitory effect with Ki or IC_{50} values of 5.28 µM (OCT2), 60.1 µM (OATP1B3), 8.05 µM (MATE1), and 7.56 µM (MATE2-K), all of which fall below the ICH M12 cut-off of 72.2 µM for CYP2C9, UGTs, and MATEs (50× Cmax,ss, unbound), 14.4 µM for OCT2 (10× Cmax,ss, unbound), and 79 µM for OATP1B3 (10× Cu,inlet). Therefore, a potential clinical DDI risk between sebetralstat and substrates of these transporters cannot be excluded. A wording has been added in section 4.5 of the SmPC.

Regarding inhibition of and BCRP in the intestinal level, this could be ruled out taking into account the limited solubility. The same for the OAT1/3 where the IC_{50} values were above the cut-off of 14. 4µM. The potential for sebetralstat to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 was assessed in an in vitro study (Study 181759) using plated human hepatocytes from three donors. Six concentrations, ranging from 1 to 200 µM, were tested, covering the worst-case scenario at systemic levels (72.24 µM), though not at intestinal levels (i.e., 244.14 µM). This was deemed acceptable due to the low solubility of sebetralstat. The control substrates, inducers, and incubation time (72 hours) were appropriate. Hepatocyte viability ranged from 84% to 96% at 100 µM when compared to vehicle controls, though vehicle treatment alone showed a marked reduction in viability (62.6% compared to media controls). As a result, 1, 10, and 100 µM of sebetralstat were selected for the CYP induction assay, and the vehicle concentration was reduced to 0.1% DMSO to minimise its effect on cell viability.

The results showed that sebetralstat induced all tested CYP enzymes at the highest concentration (100 µM) but not at concentrations below 10 µM, except for CYP3A4, which exhibited a 1.8- to 5.6-fold induction at 10 µM compared to vehicle controls. From a clinical perspective, given the intermittent use of sebetralstat and its rapid absorption and elimination, the risk of CYP induction is unlikely to be clinically significant.

However, in line with EMA guidelines on DDI and the presentation of study results in the SmPC, the in-vitro evidence indicating that sebetralstat induces CYP3A4 should be reflected in the SmPC. While this induction is not expected to have clinical relevance under the approved dosing regimen, this information remains important for potential future therapeutic scenarios or dose modifications. Therefore, it has been added to section 5.2 of the SmPC.

Berotralstat, used as a concomitant prophylactic medication in HAE patients, is primarily metabolised by the CYP3A4 enzyme and acts as a moderate CYP3A4 inhibitor. The applicant’s conclusion that sebetralstat is unlikely to exert any clinically significant CYP-mediated effects on the PK of berotralstat, or vice versa, thereby not requiring dose adjustments, is supported. However, given that berotralstat has a reported effect on QTc prolongation risk, and the QTc study for sebetralstat was also deemed positive, the co-administration of these two drugs may pose an increased risk for QTc prolongation. Furthermore, when combined with hepatic impairment and/or the use of a CYP3A4 inhibitor, the risk may be further elevated due to potential increases in the concentrations of both drugs. An appropriate warning in the SmPC has been implemented in section 4.4 of the SmPC.

Pharmacodynamics

The applicant presented the pharmacodynamics properties of sebetralstat. By blocking prekallikrein (pKa), sebetralstat prevents the cleavage of high-molecular weight kininogen (HK) into bradykinin and thus prevents the bradykinin-mediated vascular permeability. The choice of investigating the pharmacodynamics properties of sebetralstat with assays on pKa enzyme activity and inhibition of pKa cleavage of HK is therefore considered appropriate.

The applicant provided pharmacodynamics results and observations from dedicated studies to determine PKa enzyme activity in plasma samples from healthy subjects (studies KVD900-101, KVD900-102 and KVD900-110) and hereditary angioedema patients (study KVD900-201). According to the study results, it can be concluded that there have been no meaningful differences observed in the PD profile between healthy subjects and patients with HAE.

For both 300 mg and 600 mg doses, a geometric mean inhibition of PKa >90% was achieved by 30 minutes and was maintained above 95% for at least 3 to 4 hours. The PKa enzyme activity gave a similar profile at a similar dose level without significant differences between healthy subjects and patients, and gave a similar profile in the Chinese, Japanese and Caucasian ethnicities at each dose level. The results from these studies clearly indicate that a high level of PKa inhibition is rapidly achieved following oral administration of the 300 mg and 600 mg of sebetralstat.

Also the profile of inhibition of enzyme activity was unaffected by the formulation of sebetralstat (formulated tablet or powder in capsule).

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

Results also showed that >90% mean inhibition of PKa was maintained for 10 to 12 hours post-dose, when KVD900 was administered at dose intervals between 2 and 4 hours. Mean maximal inhibition of PKa activity was >98%. The suppression of release of bradykinin (BK) was measured through the inhibition of PKa cleavage of endogenous HK to cHK (cleaved HK), cHK having been as a surrogate marker for BK, as BK has a very short half-life of 60 seconds. The 600 mg dose level of sebetralstat rapidly led to inhibition of HK cleavage in the activated plasma samples, 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). The applicant did not intend however to fully determine the relationship between the pharmacodynamics and the pharmacokinetics properties of sebetralstat. No proportionality trial was conducted and the applicant stated instead that PK modelling provided supportive data on proportional activities with 300 and 600 mg, which was not considered as a sufficient approach. While it is unclear in the absence of the investigation on a potential PK exposure-effect relationship whether the 300 mg dose would be optimal it is nevertheless considered that the adequacy of the dosing is supported by the clinical study results.

Data from the pivotal study (KVD900-301) clearly demonstrated that no significant symptom relief was observed within the first hour post-dose. However, within the two-hour post-dose period, statistically significant symptom relief was evident for the 300 mg dose (but not for the 600 mg dose). These findings indicate that a time period of over one hour, corresponding to the sebetralstat T_{max}, is required for patients to be able to reliably assess symptom improvement and determine whether an additional dose is necessary.

Furthermore, PD data showed that the mean inhibition of DXS-activated PKa activity in plasma remained above 95% for 3 to 4 hours at dose levels of 300 mg and 600 mg. This suggests that taking an additional dose too soon after the first one may not provide added efficacy benefits. Administering two sequential

300 mg doses (one dose initially and a second after 3 hours if needed), extends the drug's effect by prolonging the time of maximal inhibition of DXS-activated PKa activity (as studied in KVD900-102). This approach also allows patients adequate time to assess symptom relief before deciding on an additional dose. For patients with HAE experiencing an attack, the timeframe for assessing the efficacy of sebetralstat and determining the need for an additional dose must be clearly defined. Therefore, the posology section 4.2 of the SmPC has been updated recommending that a second 300 mg dose may be taken 3 hours after the first dose, in line with the conditions of clinical trial KONFIDENT KVD900-301. A wording was also added to recommend that no more than two 300 mg doses should not be taken within 24 hours.

Regarding secondary pharmacology, potential genetic differences in PD response were not addressed by the applicant. This is acceptable as there are no genetic markers currently used to guide treatment selection for HAE patients.

The applicant was asked to address potential PD interactions with kallikrein inhibitors, such as berotralstat or lanadelumab, which may be used concomitantly as prophylactic treatment. The applicant clarifies that there was no safety concern to be expected from this combination, given that the T_{max} for both products do not overlap. This rationale is acceptable.

2.6.4. Conclusions on clinical pharmacology

The applicant performed a PD assessment of sebetralstat using a clinically relevant biomarker, but no PK/PD-based justification was provided as no dedicated study was performed. The DDI studies were adequate.

Overall, the clinical pharmacology profile is considered acceptable.

2.6.5. Clinical efficacy

Relevant clinical efficacy study comes from the Phase 3 pivotal trial, KVD900-301, with supportive clinical efficacy from the completed Phase 2 KVD900-201 trial-Part 2 and the ongoing Phase 3 KVD900 302 trial as of a data cutoff date of 31 Jan 2024 (data fully cleaned to 15 Dec 2023). Additional data are provided in response documentation from KVD900 302 trial with data lock point on 14 September 2024.

Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
KVD900-**201 (supportive)**	**Completed** First Subject Visit: 02 July 2019 Last Subject Completed: 08 December 2020 Screened : 84 Randomised : 68	Phase 2, randomised, double-blind, placebo controlled, crossover, multicentre trial conducted in 2 parts	Part 1: Open-label sebetralstat 600 mg film-coated tablets; single administration; oral Part 2: Sebetralstat 600 mg film-coated tablets; single administration	Male and female patients 18 years of age and older with a confirmed diagnosis of HAE type 1 or 2 **Attacks not eligible are**

	Received ≥1 Administration of IMP: Part 1: 68 Part 2: 53 (25 sebetralstat, 28 placebo)		before or after placebo (separated by washout); oral Matching placebo	1° Attacks involving the neck and above 2° Severe attacks
KVD900-**301 (pivotal)** KONFIDENT)	**Completed** First Subject Visit: 23 Feb 2022 Last patient Last visit 31 Dec 2023 Screened : 158 Received ≥1 Administration of IMP: 110 86 / 300 mg sebetralstat; 93 / 600 mg sebetralstat; 83 / placebo	Phase 3, double-blind, randomised, placebo controlled, three-way crossover, multicentre trial	Up to two administrations of blinded IMP administered at least 3 hours apart: sebetralstat 300 mg tablet plus placebo tablet, 600 mg tablets, or two matching placebo tablets in response to each qualifying attack of HAE If needed (as determined by the patient), a second administration of IMP (of the same assigned treatment) may have been administered for each attack at least 3 hours after the first administration; oral Matching placebo	Male and female patients 12 years of age and older with a confirmed diagnosis of HAE type 1 or 2 **Attacks not eligible are** Severe laryngeal attacks
KVD900-**302 (supportive)**	**Ongoing** First Subject Visit: 21 Oct 2022 Data Cut-Off Date: 31 Jan 2024 Screened : 118 Received ≥1 Administration of IMP: 84[a] (as of date of data cutoff for the interim analysis) [Of the 118 patients screened in KVD900 302, 68 patients were in	Phase 3, open-label multicentre, long-term safety trial	Single administration of sebetralstat 600 mg tablets to treat each HAE attack. If needed (as determined by the patient), a second administration may be administered for each attack at least 3 hours after the first administration. Patients may also use sebetralstat as a short-term prophylactic therapy prior to undergoing surgical,	Male and female patients 12 years of age and older with a confirmed diagnosis of HAE type 1 or 2 Includes patients who were randomised in KVD900-201, patients who were randomised in KVD900 301, and patients who did not participate in either trial **All attack locations and severity were eligible, including**

	the rollover group, 50 patients were in the non-rollover group (including 2 patients who had been randomised in KVD900-201 and 48 patients who were sebetralstat naïve]		dental, or medical procedures: three administrations of sebetralstat in a 24-hour period as short-term prophylaxis, with each administration approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure	**severe or very severe laryngeal attacks**

2.6.5.1. Dose response studies

Sebetralstat has been studied at doses ranging from 5 mg to 1,200 mg (maximum total daily dose 3,000 mg). The Phase 1 development work supported doses up to 600 mg. Only two studies (KVD900-101 and KVD900-110) included both a 300 mg and a 600 mg doses of sebetralstat.

Sebetralstat has been studied at doses ranging from 5 mg to 1,200 mg (maximum total daily dose 3,000 mg) in two Phase 1.

In KVD900-101 Part A when administered as single-doses of 5 – 600 mg KVD900 capsules, sebetralstat was rapidly absorbed with a median T_{max} of 0.625 – 1.00 h, more than 50% inhibition of plasma kallikrein enzyme activity was observed for 8 and 10 h following 300 and 600 mg KVD900 capsules respectively, and C_{max} was proportional to dose across the dose range, but overall exposure (AUC) was greater than proportional to dose.

In KVD900-110 following single oral doses of 300 mg, 600 mg, and 1,200 mg KVD900, T_{max} was not dose dependent and was comparable across the ethnic populations (White, Japanese and Chinese).

2.6.5.2. Main study

KVD900-301 KONFIDENT

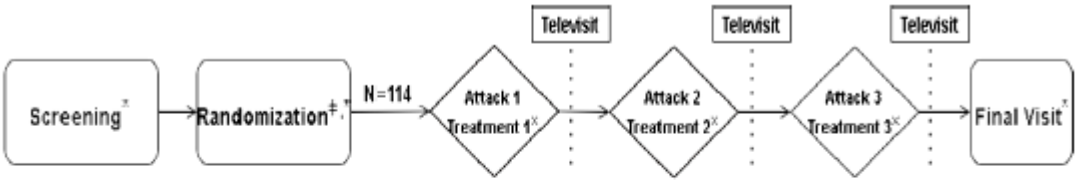
Methods

KVD900-301 is a randomised, double-blind, placebo-controlled, phase 3, multicentre clinical trial, three-way crossover trial to evaluate the efficacy and safety of two dose levels of KVD900 (300 mg and 600 mg), an oral plasma kallikrein inhibitor, for on-demand treatment of angioedema attacks in adolescent (≥12 to <18 years) and adult patients with hereditary angioedema type 1 or 2.

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 Treatment Period will begin when the first HAE eligible attack occurs. Patients will treat 3 separate, eligible HAE attacks with their assigned IMP treatment for that attack.

Figure 2. Schematic of Trial Design



Notes: *if in-clinic visits were not possible (eg, in the event of a pandemic, or other reasons that prevent the patient from attending in-clinic visits), home health visits were to be permitted in place of in-clinic visits. Information captured during a home health visit would mirror that captured in an in-clinic visit.
*The Randomization Visit may have occurred as a televisit or in-clinic visit.
* Patients were to contact a call center after the initial dose of IMP, prior to a second dose of IMP, and prior to a dose of conventional on-demand treatment for each treated attack.

- **Study Participants**

The trial population included male and female patients 12 years of age and older with a confirmed diagnosis of HAE type 1 or 2 and without severe laryngeal attacks.

The trial population comprised 2 subsets:

- patients who entered the trial taking only conventional on-demand treatment;
- patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

Main Inclusion Criteria

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

2. Confirmed diagnosis of HAE type 1 or 2

3. Patient had access to and ability to use conventional on-demand treatment for HAE attacks.

4. If a patient was 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 screening visit and be willing to remain on a stable dose and regimen for the duration of the trial.

5. Patient's last dose of attenuated androgens was at least 28 days prior to randomisation.

6. Patient:

    a. had at least 2 documented HAE attacks within 3 months prior to screening or randomisation; or

    b. was a completer of the KVD824-201 trial within 3 months prior to randomisation and met all other entry criteria to enrol 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. 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.

3. Use of ACE inhibitors after the screening visit or within 7 days prior to randomisation.

4. Any oestrogen-containing medications with systemic absorption (such as oral contraceptives including ethinyloestradiol or hormonal replacement therapy) within 7 days prior to the screening visit.

5. Patients who required sustained use of strong cytochrome P450 3A4 inhibitors or inducers.

6. Inadequate organ function,

7. Any clinically significant comorbidity or systemic dysfunction,

8. Prior participation in KVD900-201 trial.

- **Treatments**

KVD900 (sebetralstat) was formulated as 300 mg KVD900 film-coated tablets for oral use. Patients were to self-administer a single oral dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 600 mg KVD900 (2 × 300 mg KVD900 tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP could be administered for each attack.

Mild and moderate laryngeal attacks could be treated in KVD900-301, and patients were instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsened.

Patients were to treat as soon as possible after recognition of the start of the attack. Patients treated each attack with up to 2 of doses IMP, administered at least 3 hours apart. Eligible attacks should initially be treated with a single administration of IMP.

Attacks that did not meet eligibility could be treated with conventional on-demand treatment per the patient's usual treatment regimen.

- **Objectives**

The primary objective was to show statistical superiority of each dose of KVD900 versus placebo on the primary endpoint (time to beginning of symptom relief defined by the PGI-C as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration).

The null hypothesis was that there is no difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration (no difference between each dose of KVD900 group versus placebo) versus the alternative hypothesis that the survival distributions are different (each of the KVD900 treatment groups versus placebo).

Estimands for primary objective

Population	**Adolescent and adult patients with hereditary angioedema type 1 or 2**
Treatment condition<s>	Initially, a single dose of KVD900 300 mg, 600 mg, or matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), a second dose of IMP may be administered for each attack. Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.
Endpoint (variable)	The 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.
Population-level summary	Difference in median time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration.
Intercurrent events and strategy to handle them	
IcEV1 (discontinue due to any reason)	Hypothetical. Assume that an intercurrent event would not have occurred. Discontinued patients are censored at time of discontinuation (taken from last assessment done during the end of study visit).
IcEV2 (Prohibited medications)	Treatment policy. Assessments made after prohibited medication use(s) will be included in the analyses regardless of the medication use(s).
IcEV3 (Conventional Attack treatment)	Composite. Receiving conventional attack treatment prior to the beginning of symptom relief for an eligible attack will be considered as treatment failure; patients receiving conventional attack treatment will be censored at 12 hours for the impacted attack.

The key secondary objectives were to show statistical superiority of each dose of KVD900 versus placebo on the key secondary endpoints (time to first incidence of decrease from baseline as defined by PGI-S for two time points in a row within 12 hours of the first IMP administration and time to HAE attack resolution defined as "none" on PGI-S within 24 hours of the first IMP administration without conventional attack treatment use).

The null hypothesis for key secondary objectives was that there is no difference in survival distributions of the time to event endpoints (no difference between each dose of KVD900 group versus placebo) versus the

alternative hypothesis that the survival distributions are different (each of the KVD900 treatment groups versus placebo).

Estimands for key secondary 1 objective

Population	Adolescent and adult patients with hereditary angioedema type 1 or 2
Treatment condition<s>	Initially, a single dose of KVD900 300 mg, 600 mg, or matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), a second dose of IMP may be administered for each attack. Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.
Endpoint (variable)	The PGI-S: time to first incidence of decrease from baseline for two time points in a row within 12 hours of the first IMP administration.
Population-level summary	Difference in median time to first incidence of decreases from baseline for 2 time points in a row in PGI-S within 12 hours of the first IMP administration.
Intercurrent events and strategy to handle them	
IcEV1 (discontinue due to any reason)	Hypothetical. Assume that an intercurrent event would not have occurred. Discontinued patients are censored at time of discontinuation (taken from last assessment done during the end of study visit).
IcEV2 (Prohibited medications)	Treatment policy. Assessments made after prohibited medication use(s) will be included in the analyses regardless of the medication use(s).
IcEV3 (Conventional Attack treatment)	Composite. Receiving conventional attack treatment prior to the first incidence of PGI-S decreases for an eligible attack will be considered as treatment failure; patients receiving conventional attack treatment will be censored at 12 hours for the impacted attack.

Estimands for key secondary 2 objective

Population	Adolescent and adult patients with hereditary angioedema type I or II
Treatment condition<s>	Initially, a single dose of KVD900 300 mg, 600 mg, or matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), a second dose of IMP may be administered for each attack. Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.
Endpoint (variable)	The PGI-S: Time to HAE attack resolution defined as "none" on PGI-S within 24 hours of the first IMP administration without conventional attack treatment use.
Population-level summary	Difference in median time to first incidence of decreases from baseline for 2 time points in a row in PGI-S within 12 hours of the first IMP administration.
Intercurrent events and strategy to handle them	
IcEV1 (discontinue due to any reason)	Hypothetical. Assume that an intercurrent event would not have occurred. Discontinued patients are censored at time of discontinuation (taken from last assessment done during the end of study visit).
IcEV2 (Prohibited medications)	Treatment policy. Assessments made after prohibited medication use(s) will be included in the analyses regardless of the medication use(s).

Population	Adolescent and adult patients with hereditary angioedema type I or II
IcEV3 (Conventional Attack treatment)	Composite. Receiving conventional attack treatment prior to the attack resolution for an eligible attack will be considered as treatment failure; patients receiving conventional attack treatment would be censored at 24 hours for the impacted attack.

- **Outcomes/endpoints**

Primary Objective and Endpoint (PGI-C / Patient Global Impression of Change)

- Primary objective: the primary objective was to demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.
- Primary 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 / Patient Global Impression of Severity)

- PGI-S: Time to first incidence of decrease in severity 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

- **Sample size**

A total sample size of approximately 114 patients were to be randomised 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.

Based on results from the Phase 2 trial (KVD900-201), a sample size of 66 patients completing the trial would provide 90% power for testing each pairwise comparison (KVD900 versus placebo) at the 2.5% alpha level (2-sided) for the primary endpoint of time to beginning of symptom relief of the HAE attack as defined by PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration. This sample size was derived using the assumption that median time to symptom relief of the HAE attack is 1.6 hours in active dose arm and 9 hours in placebo arm from trial KVD900-201. It was assumed that patients begin the trial together and will be followed for the same period of time, 49% of patients in control group and 17% of patients in KVD900 treatment group were assumed to be lost-to-follow-up (right-censored). Using conservative approach and simulation-based procedure for power calculations for a parallel group design, the two-sided two-group survival comparison Gehan-Wilcoxon test had approximately 90% power to detect a median time ratio of 5.6 (9/1.6) with a target 2-sided significance level of 2.5% for 66 patients in each treatment group.

The treatment effect observed in the Phase 2 (KVD900-201) trial was assumed to be representative of the entire KVD900-301 population. However, additional trial populations were enrolled (e.g., adolescent patients and patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment) where the treatment effect had not been previously characterised. Therefore, a total of 84 patients completing the trial was proposed (to ensure approximately 84 attacks treated with placebo, 300 mg KVD900 and 600 mg KVD900). This conservative approach increased the likelihood of maintaining at least 90% power in the event that the true treatment effect in the KVD900-301 population was different to that observed in the KVD900-201 trial.

Assuming there would be approximately 30% dropout or non-completion rate, consistent with the Phase 2 trial, the oversampling by 30 patients (84 + 30 = 114) was proposed to account for patients who may not complete all treatment periods due to infrequent or ineligible HAE attacks or for patients who discontinue the trial early, for whatever reason, and ensure sufficient attacks were treated.

- **Randomisation and Blinding (masking)**

Randomisation

Patients were assigned to receive 3 treatments in randomised crossover fashion based on their assignment to 1 of 6 treatment sequences. Randomisation was stratified by whether the patient enters the trial taking only conventional on-demand treatment vs. on a stable dose and regimen of long-term prophylactic treatment.

Randomisation occurred using a Randomisation and Trial Supply Management System in a 1:1:1:1:1:1 ratio using a permuted-block randomisation method to ensure a balanced assignment to each treatment sequence. A sample randomisation schedule is presented below.

Treatment Sequence	1st Eligible HAE Attack	2nd Eligible HAE Attack	3rd Eligible HAE Attack
A	Placebo	600 mg	300 mg
B	Placebo	300 mg	600 mg
C	300 mg	600 mg	Placebo
D	300 mg	Placebo	600 mg
E	600 mg	300 mg	Placebo
F	600 mg	Placebo	300 mg

Blinding

This trial was performed in a double-blind, double-dummy manner. The trial blind was not to be broken except for any medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g. for SAEs or death).

- **Statistical methods**

Analysis populations

Full Analysis Set: The FAS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses.

Per-Protocol Set: The PPS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack and who did not have major protocol deviations that could affect the primary efficacy endpoint.

Primary endpoint

The null hypothesis was that there is no difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration (no difference between each dose of KVD900 group versus placebo) versus the alternative hypothesis that the survival distributions are different (each of the KVD900 treatment groups versus placebo).

• $H0$: $tk - tp = 0$,

• Ha: $tk - tp \neq 0$.

Where tk was the time to "a little better" or higher rating of HAE attack following KVD900 dose treatment and tp was the time to "a little better" or higher rating of HAE attack following placebo.

Attacks were treated as right-censored at 12 hours if they did not achieve beginning of symptom relief defined by PGI-C as at least "a little better" (2 time points in a row) or received conventional attack treatment prior to time-to-event within 12 hours of the first IMP administration. In the case of discontinuation that prevented event "a little better" or higher HAE attack rating occurrence, patients were censored at the time of discontinuation (taken from last assessment done during the final/ET visit).

In the case of underivable time-to-event results due to lack of at least 2 consecutive post-baseline assessments, attacks were censored at time 0.

Time to beginning of symptom relief defined as at least "a little better" for 2 time points in a row on the PGI-C within 12 hours of IMP administration was analysed using Gehan score transformation test.

To perform the test, each observation was transformed to Gehan score. For each pairwise comparison, Gehan score for the ith observation was the number of observations in the entire data set clearly smaller than the ith minus the number clearly larger. That is,

• For uncensored observations, the Gehan score was the number of uncensored observations strictly smaller, minus the number of uncensored observations strictly greater, minus the number of right-censored observations equal or greater.

• For right-censored observations, the Gehan score was the number of uncensored observations smaller or equal.

Gehan scores were analysed using a linear mixed model, including terms for sequence, period and treatment in the model as fixed effects and patient nested within sequence as a random effect. Least-squares means of treatment effects to show differences between treatments (600 mg KVD900 versus placebo and 300 mg KVD900 versus placebo) were tested at alpha of 0.025 level. Least-squares means and standard errors were presented by treatment. P-values calculated for the comparison of each KVD900 dose versus placebo, along with the least-square mean treatment difference and corresponding 95% CI were presented. Additionally, adjusted p-values for each pairwise comparison were presented with Bonferroni adjustment and loop-back feature.

Kaplan-Meier estimates of the 25th percentile (Q1), the median and the 75th percentile (Q3) and corresponding 95% CI of time to beginning of symptom relief were presented by treatment. Kaplan-Meier survival curves were presented by treatment.

Sensitivity analyses

Imputation Under Informative Censoring

For this first sensitivity analysis, censored observations were treated as missing data. Parametric multiple imputation under informative censoring assumption was applied to impute censored data. Informative censoring assumes correlation between failure and censoring time (Taylor et al 2002; O'Connor 2020). Censored or missing outcome values were imputed from a distribution derived from remaining at risk patients under various assumptions of the correlation between censoring and outcome. The first steps of the imputation method were to identify this distribution, followed by the random selection of the imputed value until new multiple imputed data set was created. The procedure was independently repeated 100 times

creating 100 imputed data sets. The primary analysis was repeated on each of the 100 multiply imputed data sets and the results were combined using Rubin's method from PROC MIANALYZE.

Gehan's Generalised Wilcoxon Test Sensitivity Analysis

This nonparametric test for comparing time-to-event data was an extension of the Wilcoxon rank sum test in the presence of censoring. The test was designed for crossover studies with 2 sequences.

For this sensitivity analysis, assuming no period effect, two separate 2x2 crossover designs with a common placebo was constructed. The first crossover trial was for 300 mg KVD900 versus placebo and the second crossover trial was for 600 mg KVD900 versus placebo. In this analysis, the sequence with KVD900-treated period prior to the placebo-treated period was pooled into a new active-placebo sequence; the sequence with KVD900-treated period after the placebo-treated period was pooled into a new placebo-active sequence.

Supplementary analyses

Supplementary analyses were performed in the FAS and PPS.

• The primary endpoint analysis was repeated in the PPS. The time to beginning of symptom relief within 12 hours (by considering censoring rules also) was categorised into intervals (0 to 1, >1 to 2, >2 to 4, >4 to 6, >6 to 8, >8 to 10, and >10 to 12 hours) and the number and percentage of attacks that fell into each category was presented. If several categories had 0 counts, wider intervals (0 to 4, >4 to 8, >8 to 12 hours) were considered. In addition, the time-to-event analysis was conducted for time intervals within 1, 2, 4, 6, 8, 10, and 24 hours of the first IMP administration (similar to the analysis performed for the within 12 hours of the first IMP administration interval).

• The outcomes of patients who took conventional attack treatment were imputed with a hypothetical strategy, i.e., their time to beginning of symptom relief defined as at least "a little better" (2 times in a row) within 12 hours of IMP administration on the PGI-C was imputed as right-censored at the time of conventional attack treatment. The primary analysis was then repeated.

<u>Key secondary endpoints</u>

The key secondary endpoints were analysed in a similar manner as for the main analysis of primary endpoint, as described above.

<u>Other secondary endpoints</u>

Time to event endpoints

All time to event endpoints were analysed similarly as described for the primary endpoint analysis. Subjects were right-censored if no events by the end of the relevant analysis period (at the corresponding time point). The right-censoring at the end of the analysis period in case of conventional attack treatment was not applicable to the following endpoints: Time to either (1) first incidence of PGI-C being rated 'a little worse' or lower for 2 time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours; Time to either (1) first incidence of worsening in attack severity on the PGI-S by one level or more from baseline for 2 time points in a row, or (2) use of conventional attack treatment, whichever comes first within 12 hours and 24 hours; Time to first incidence of conventional attack treatment use within 12 hours and 24 hours. For the time to second IMP administration, patients who received conventional medication prior to second IMP use were censored at the time of conventional medication use.

Number and percentage of attacks with beginning of symptom relief for 2 time points in a row within 2, 4, 6, 8, 10, 12, 24, and 48 hours of the first IMP administration

Number and percentage of attacks with beginning of symptom relief was defined as at least "a little better" (2 time points in a row without possible missing values in between) within 2, 4, 6, 8, 10, 12, 24, and 48 hours of the first IMP administration and was analysed descriptively.

Attacks that did not have at least 2 post-baseline assessments within the analysed period were excluded from this analysis. Patients who discontinued or received conventional attack treatment prior to time-to-event during a time period were considered as non-responders for that period. The number and percentage of attacks achieving beginning of symptom relief were presented by time point and treatment. Risk difference comparing each active KVD900 treatment to the placebo treatment, and corresponding exact 95% CI (Santner and Snell 1980) were provided.

Number and percentage of attacks with second IMP administration within 4, 8, 12, 24, and 48 hours of the first IMP administration

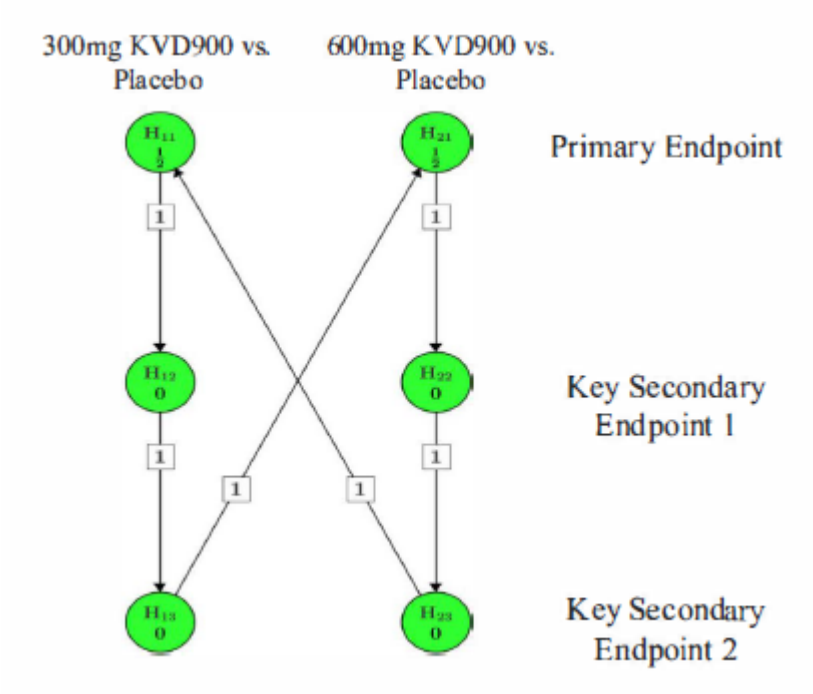
The number and percentage of attacks with second IMP administration within 4, 8, 12, 24, and 48 hours of the first IMP administration was analysed descriptively.

Patients who discontinued or received conventional medication prior to time-to-event during a time period were considered as non-responders for that period. The number and percentage of patients who used second IMP administration or conventional treatment was presented by time point and treatment. Risk difference comparing each active KVD900 treatment to the placebo treatment, and corresponding exact 95% CI were provided.

Multiplicity adjustment

Two pairwise comparisons were performed: 300 mg KVD900 versus placebo and 600 mg KVD900 versus placebo. All statistical tests were 2-sided with an overall alpha of 0.05. The primary efficacy endpoint and key secondary endpoints analysis had Bonferroni multiplicity adjustment for multiple dose levels with a loop-back feature to allow two-way alpha passing (FDA 2022). Therefore pairwise comparison tests were 2-sided with an alpha of 0.025 initially. If the primary and key secondary endpoints hypotheses within one of the pairwise comparison were not all rejected at 0.025 alpha level, but the hypotheses for the other pairwise comparison were all rejected, then the unused alpha from the rejected hypotheses was to be directed to loop-back to the unrejected hypotheses, which was then retested at the higher alpha level of 0.05. The outputs presented actual p-values and adjusted p-values.

Within each pairwise comparison, fixed sequence closed testing procedure was to be followed. The fixed testing procedure was to be employed first on the primary and then on the key secondary endpoints 1 and 2, separately for each dose comparison to placebo. Specifically, key secondary endpoint 1 was tested only if the test on the primary endpoint was statistically significant. Key secondary endpoint 2 was tested only if the test on the primary and key secondary endpoint 1 were statistically significant.



Changes to planned analyses

There were several global protocol amendments (4 global versions in total) and two versions of statistical analysis plans (v1 on 30 June 2023 and v2 on 1 December 2023). First patient first visit was on 23 February 2022 and last patient last visit on 31 December 2023.

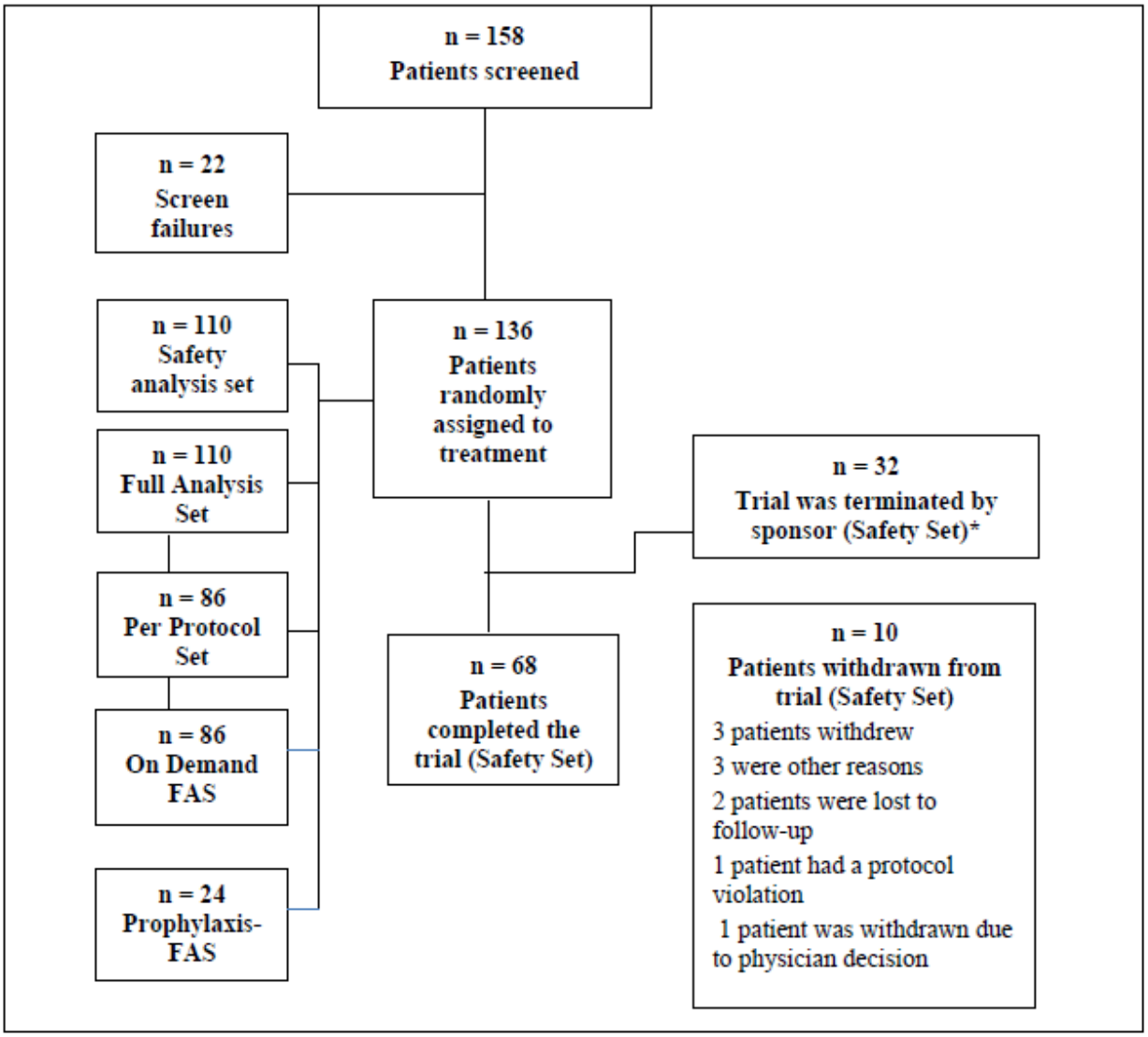
The following aspects of the planned analyses were modified after first patient first visit as part of protocol global amendments.

Protocol version	Change to the planned analyses
Protocol Version 4.0 (26 April 2023)	Modified the censoring strategy for conventional on-demand treatment from a hypothetical strategy to a composite strategy (per FDA recommendation) Changed the Full Analysis Set definition from requiring IMP treatment for at least 2 periods to just 1 period. Added alpha loop-back feature in the multiplicity adjustment strategy. Updated key secondary endpoint #1 to assess sustained improvement by requiring at least 2 time points in a row with the same (or better) measurement (per FDA recommendation) Added additional subgroup analyses to investigate consistency in treatment effects in additional subgroups and clarified that additional endpoints may be added to the statistical analysis plan.

Results

- **Participant flow**

158 patients were screened. A total of 136 patients were randomly assigned to receive the IMP, of which a total of 110 patients treated at least 1 attack with IMP and were therefore included in FAS and the Safety Set; 86 patients were included in PPS. Of the 110 patients included in the FAS and Safety Set, this included 13 paediatric patients that were evaluable for the primary analysis.



- **Recruitment**

First patient first visit: 23 Feb 2022

Trial Completion Date: Last patient last visit: 31 Dec 2023

- **Conduct of the study**

Please see above Changes to planned analyses

- **Baseline data**

Demographic and Baseline Characteristics (Safety Set)

	Total (N=110)
Age (years)	
Mean (SD)	37.7 (14.96)
Median	39.5 (13, 74)
Q1, Q3	25.0, 49.0
Min-max	13-74
Sex, n (%)	

	Total (N=110)
Male	44 (40.0)
Female	66 (60.0)
Race, n (%)	
White	92 (83.6)
Black or African American	1 (0.9)
Asian	10 (9.1)
Other	1 (0.9)
Not reported	6 (5.5)
Ethnicity, n (%)	
Hispanic	7 (6.4)
Latino Not	95 (86.4)
Hispanic or Latino Not	8 (7.3)
Weight (kg)	
Mean (SD)	77.86 (19.179)
Median	73.30
Q1, Q3	65.00, 91.60
Min-max	41.0-140.3
Body mass index (kg/m2)	
Mean (SD)	27.44 (6.261)
Median	26.24
Q1, Q3	22.85, 31.65
Min-max	18.2-45.6

Baseline Hereditary Attack Characteristics (FAS 110 patients)

A total of 264 attacks were treated and included in the FAS, of which 87 in the 300 mg KVD900 group, 93 in the 600 mg group, and 84 in the placebo group. The baseline characteristics of the treated attacks included all attack severities (but none-very severe) and locations (abdominal, subcutaneous, laryngeal, and mixed). Baseline characteristics for IMP-treated attacks were similar across the treatment groups.

The majority of treated attacks were of mild (113 [42.8%]) or moderate (102 [38.6%]) severity on the PGI-S at the time of treatment. Thirty-eight (14.4%) attacks were severe and 7 (2.7%) were very severe at the time of treatment.

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 [range: 6.0 to 130], 41 minutes for the 600 mg KVD900 group [range: 5.0 to 142], and 51 minutes for the placebo group [range: 6.0 to 166]).

The representativeness of the 2 types of angioedema in the adult population is respected, with 91.8% type 1 and 8.2% type 2. Children are all HAE type 1, which is certainly linked to the low number of adolescents.

The most common concomitant medications were haematologics taken by 43 (39.1%) patients, other analgesics and antipyretics by 17 patients (15.5%), and anti-inflammatory and antirheumatic products, non-steroids by 14 patients (12.7%), and antihistamines for systemic use by 12 patients (110.9%). The most common concomitant medications by preferred term included complement C1 esterase inhibitor (16 [14.5%] patients), and icatibant (17 [15.5%] patients). Berotralstat and lanadelumab were used by 10 (9.1%) of patients each.

Most sebetralstat-treated attacks were treated with a single IMP administration: 53 attacks (61.6%) treated with 300 mg, 56 attacks (58.9%) treated with 600 mg, and 37 attacks (44.6%) treated with placebo. If needed (as determined by the patient), an optional additional administration could have been taken for each

attack. A second administration was used to treat the remaining 118 attacks (33 attacks [38.4%] treated with 300 mg, 39 attacks [41.1%] treated with 600 mg, and 46 attacks [55.4%] treated with placebo).

Where a second dose was taken, the median time between the 2 IMP doses was 3.858 hours for the 300 mg KVD900 group, 3.783 hours for the 600 mg KVD900 group, and 3.500 hours for the placebo group.

Table 2. Recent HAE Attack History by Background HAE Treatment Regimen

	Statistics	**On-Demand (N = 86)**	**On Kallikrein LTP (N = 19)**	**On Other LTP (N = 5)**
Number of attacks		383	73	26
Maximum Severity Category				
Mild	n (%)	122 (31.4)	29 (39.7)	2 (7.7)
Moderate	n (%)	191 (49.2)	38 (52.1)	19 (73.1)
Severe	n (%)	69 (17.8)	5 (6.8)	5 (19.2)
Very Severe	n (%)	1 (0.3)	1 (1.4)	0
Missing	n (%)	5 (1.3)	0	0
Location of Attacks				
Head/Face/Neck	n (%)	36 (9.3)	21 (28.8)	0
Torso	n (%)	19 (4.9)	7 (9.6)	0
Arms/Hands	n (%)	132 (34.0)	5 (6.8)	5 (19.2)
Genitals	n (%)	21 (5.4)	3 (4.1)	0
Legs/Feet	n (%)	109 (28.1)	11 (15.1)	11 (42.3)
Abdomen	n (%)	192 (49.5)	34 (46.6)	22 (84.6)
Larynx/Throat	n (%)	9 (2.3)	4 (5.5)	0
Pooled Attack Location 1				
Laryngeal	n (%)	9 (2.3)	4 (5.5)	0
Abdominal Only	n (%)	145 (37.4)	30 (41.1)	13 (50.0)
Subcutaneous Only	n (%)	189 (48.7)	35 (47.9)	4 (15.4)
Abdominal and Subcutaneous	n (%)	45 (11.6)	4 (5.5)	9 (34.6)
Pooled Attack Location 2				
Neck and Above	n (%)	41 (10.6)	21 (28.8)	0
Abdominal	n (%)	184 (47.4)	34 (46.6)	22 (84.6)
Other	n (%)	163 (42.0)	18 (24.7)	4 (15.4)

Participants reported their recent HAE attack history during the enrolment visit for study KVD900-301. The applicant performed an ad-hoc analysis to look into the recent HAE attack history by participants' prophylaxis treatment status (On-demand Only, On Kallikrein Long-term Prophylaxis [LTP], On Other LTP). As shown above, among all recent HAE attacks reported, the maximum severity category, locations of attack, and pooled attack locations appear to be comparable between participants on on-demand only vs. those on kallikrein LTP or other LTP.

- **Numbers analysed**

All 110 patients treated their first attack with IMP, 86 patients treated also their second attack with IMP, and 68 patients also treated their third attack with IMP, for a total of 264 treated attacks.

- **Outcomes and estimation**

PRIMARY ENDPOINT (PATIENT GLOBAL IMPRESSION OF CHANGE)

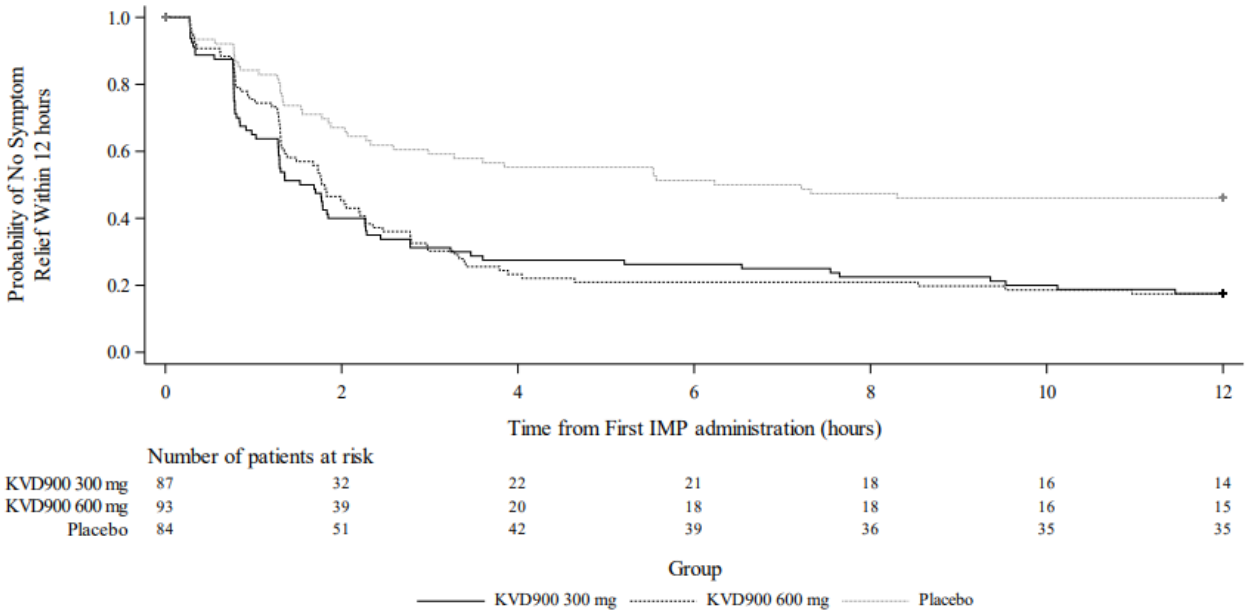
The analysis of the primary end point corresponding to time to the beginning of symptom relief defined as at least "a little better" (2 time points in a row) on the PGI-C within 12 hours of the first IMP administration using the Gehan score transformation test for FAS is presented in Table 3 and Figure 3.

Table 3. KVD900-301 -Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to Beginning of Symptom Relief on PGI-C within 12 Hours (Full Analysis Set)

	300 mg Sebetralstat	600 mg Sebetralstat	Placebo
n	87	93	84
Number of attacks			
Events[a]	66 (75.9)	71 (76.3)	41 (48.8)
Censored[b]	21 (24.1)	22 (23.7)	43 (51.2)
Time to beginning of symptom relief[c]			
25th percentile (95% CI)	0.78 (0.77, 0.98)	1.02 (0.78, 1.30)	1.34 (0.85, 2.07)
Median (95% CI)	1.61 (1.28, 2.27)	1.79 (1.33, 2.27)	6.72 (2.33, NE)
75th percentile (95% CI)	7.04 (2.28, NE)	3.79 (2.78, NE)	NE (NE, NE)
Gehan score LS means (SD)[d]	-29.44 (13.82)	-11.32 (13.65)	51.59 (14.51)
LS means difference from Placebo (95% CI)	-81.03 (-117.38,-44.68)	-62.91 (-98.61, -27.21)	-
Adjusted p-value (active vs. placebo)[e]	<0.0001	0.0013	-

The Kaplan-Meier plot for the time to beginning of symptom relief on PGI-C within 12 hours is presented in Figure 3. More attacks reached the beginning of symptom relief in the 300 mg KVD900 and 600 mg KVD900 treatment groups than placebo group.

Figure 3. KVD900-301 – Kaplan-Meier Plot for Time to Beginning of Symptom Relief within 12 Hours of Initial IMP Administration (Full Analysis Set)



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.

Sensitivity Analysis Results for Primary Endpoint on FAS

Gehan's Generalised Wilcoxon test sensitivity analysis is presented in Table 4.

The time to beginning of symptom relief was reached faster in the 300 mg KVD900 versus placebo group (nominal p=0.007) and 600 mg KVD900 versus placebo group (nominal p<0.0001) within the 12-hour analysis window.

Table 4. Gehan's Generalised Wilcoxon Test of Time to Beginning of Symptom Relief on PGI-C within 12 Hours (Full Analysis Set)

	300 mg KVD900 versus placebo		600 mg KVD900 versus placebo	
	300 mg KVD900 (N=110)	Placebo (N=110)	600 mg KVD900 (N=110)	Placebo (N=110)
n	71	71	76	76
Number of attacks				
Events[a]	55 (77.5)	36 (50.7)	60 (78.9)	37 (48.7)
Censored[b]	16 (22.5)	35 (49.3)	16 (21.1)	39 (51.3)
Time to beginning of symptom relief[c]				
25th percentile (95% CI)	0.79 (0.77, 1.03)	1.32 (0.79, 2.04)	1.27 (0.79, 1.33)	1.34 (0.85, 2.07)
Median (95% CI)	1.69 (1.28, 2.28)	5.57 (2.07, NE)	2.01 (1.38, 2.46)	7.32 (2.59, NE)
75th percentile (95% CI)	7.65 (2.44, NE)	NE (NE, NE)	3.84 (2.79, NE)	NE (NE, NE)
p-value (active versus placebo)[d]	0.0007		<0.0001	-

Notes: PGI-C=Patient Global Impression of Change; NE=Not evaluable

Patients with at least 2 periods, one being placebo, were included.

Time to beginning of symptom relief within 12 hours was defined as an HAE attack being rated "a little better" or higher on the PGI-C for two time points in a row within 12 hours of the first IMP administration.

Time to beginning of symptom relief was calculated as date/time of first rating of "a little better" or higher (i.e., better or much better) which is immediately followed by another rating of "a little better" or higher (without missing values in between) – Date/time of first IMP administration.

[a] Attack that achieved the described event within 12 hours.

[b] Attacks were treated as right-censored at 12 hours if they did not achieve beginning of symptom relief defined by PGI-C as at least "a little better" (2 time points in a row) or received conventional attack treatment within 12 hours of the first IMP administration. In the case of discontinuation that prevented event "a little better" or higher HAE attack rating occurrence, patients is censored at the time of discontinuation.

[c] Kaplan-Meier estimates for time to beginning of symptom relief within 12 hours.

[d] P-values from Gehan's Generalized Wilcoxon test.

Supplementary Analysis Results for Primary Endpoint on FAS

Proportion of attacks that achieved the primary endpoint without a second administration or prior to use of second administration

Given the unrestricted use of a second administration of sebetralstat in KVD900-301, the proportion of attacks that achieved the primary endpoint without a second administration or prior to use of second administration was evaluated. In KVD900-301, the percentage of attacks treated with a single administration of 300 mg, 600 mg, and placebo was 61.6%, 58.9%, and 44.6%, respectively. Although the KVD900-301 trial was not designed to compare efficacy between one versus two administrations of sebetralstat, the majority of attacks that successfully met the primary endpoint (93.9% for attacks treated with 300 mg and 95.8% for attacks treated with 600 mg) did so after a single administration.

KEY SECONDARY ENDPOINTS

Key Secondary 1 Objective / Time to Reduction in Severity (Patient Global Impression of Severity)

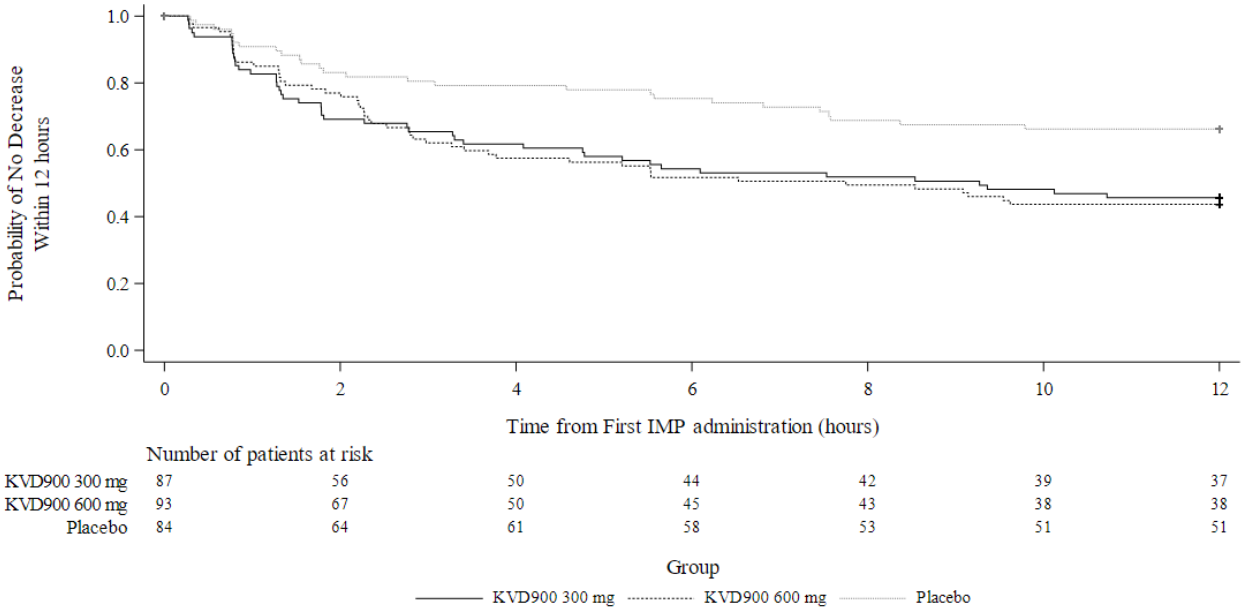
The Key Secondary 1 Objective corresponds to the time to first incidence of decrease from baseline (2 time points in a row) on the PGI-S within 12 hours of the first IMP administration.

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. (Table 5, Figure 4).

Table 5. KVD900-301 - Time to Reduction in Severity within 12 Hours of Initial IMP Administration (Full Analysis Set)

	300 mg Sebetralstat	600 mg Sebetralstat	Placebo
n	87	93	84
Number of attacks			
Events[a]	44 (50.6)	49 (52.7)	26 (31.0)
Censored[b]	43 (49.4)	44 (47.3)	58 (69.0)
Time to reduction in severity[c]			
25th percentile (95% CI)	1.53 (0.85, 2.78)	2.19 (1.30, 2.79)	6.23 (1.76, NE)
Median (95% CI)	9.27 (4.08, NE)	7.75 (3.27, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Gehan score LS means (SD)[d]	-38.01 (12.45)	-37.44 (12.08)	13.21 (12.93)
LS means difference from Placebo (95% CI)	-51.22 (83.13, -19.31)	-50.65 (-81.82, 19.48)	-
Adjusted p-value (active vs. placebo)[e]	0.0036	0.0032	-

Figure 4. KVD900-301 - Kaplan-Meier Plot for Time to Reduction in Severity within 12 Hours of Initial IMP Administration (Full Analysis Set)



Key Secondary 2 Objective / Time to Complete Attack Resolution

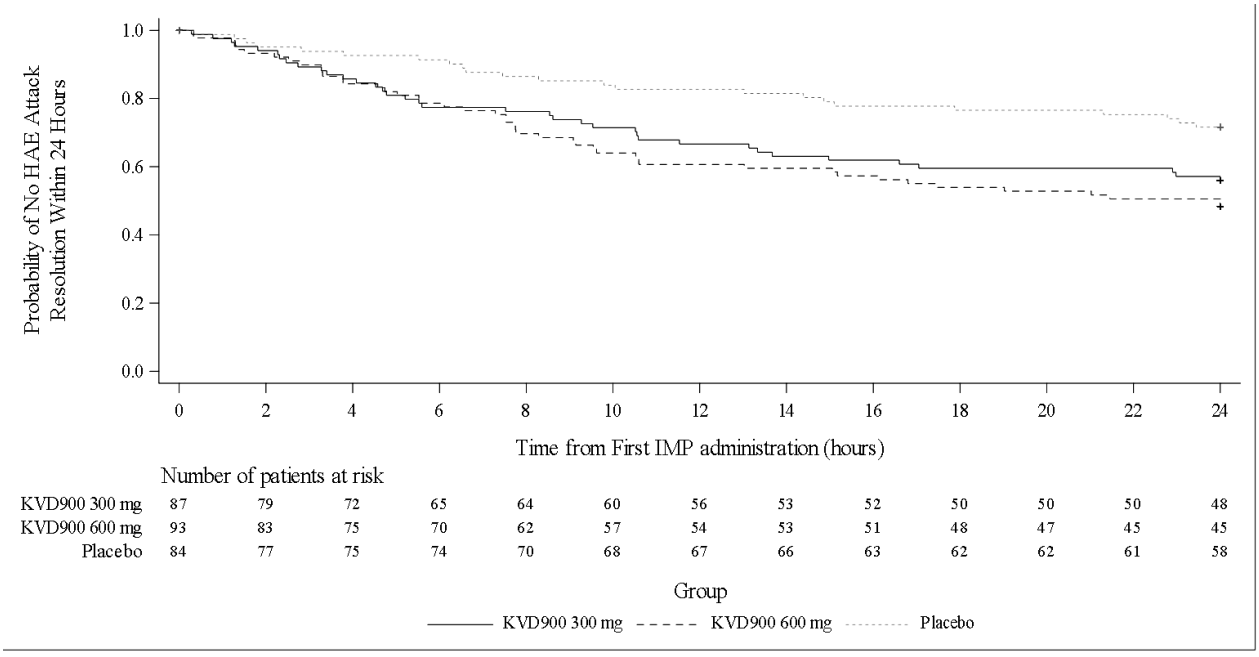
The Key Secondary 2 Objective corresponds to the time to HAE attack resolution defined as "none" on the PGI-S within 24 hours of the first IMP administration

There was a statistically significant improvement in the time to 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. (Table 6, Figure 5).

Table 6. KVD900-301 – Time to Complete Attack Resolution within 24 Hours of Initial IMP Administration (Full Analysis Set)

	300 mg Sebetralstat	600 mg Sebetralstat	Placebo
n	87	93	84
Number of attacks			
Events[a]	37 (42.5)	46 (49.5)	23 (27.4)
Censored[b]	50 (57.5)	47 (50.5)	61 (72.6)
Time to complete attack resolution[c]			
25th percentile (95% CI)	8.58 (4.08, 13.13)	7.54 (3.78, 9.55)	22.78 (9.79, NE)
Median (95% CI)	NE (16.60, NE)	24.00 (10.60, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Gehan score LS means (SD)[d]	1.62 (13.98)	-17.46 (13.62)	56.25 (14.43)
LS means difference from Placebo (95% CI)	-54.62 (-87.05, -22.19)	-73.71 (-105.35, -42.08)	-
Adjusted p-value (active vs. placebo)[e]	0.0022	<0.0001	-

Figure 5. KVD900-301- Kaplan-Meier Plot for Time to Complete Attack Resolution within 24 Hours of Initial IMP Administration (Full Analysis Set)



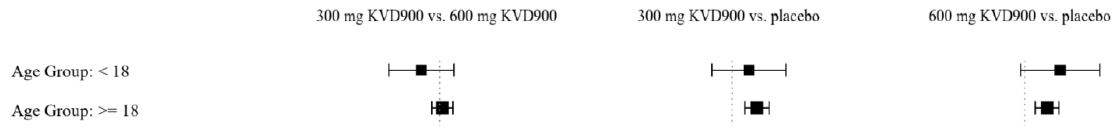
HAZARD RATIO BETWEEN TREATMENTS FOR PRIMARY AND KEY SECONDARY ENDPOINTS (KVD900-301 REPORT BODY)

The applicant has provided the requested data for all subgroups as forest plots.

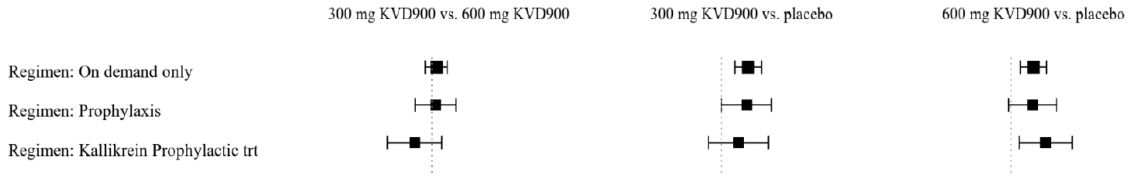
The hereafter analyses are done only with results on the primary endpoint but trends are the same for both secondary endpoints.

Race patient: this presentation validates the under-representation of people of Asian race for whom the variability of results is important. Black patients do not appear.

Age patients: results for patients aged over 18 years were fully significant against placebo for both dosages, 300 mg and 600 mg. For patients aged under 18 years, the variability of results related to the low representativeness of this age group was highlighted for the 300 mg dose.

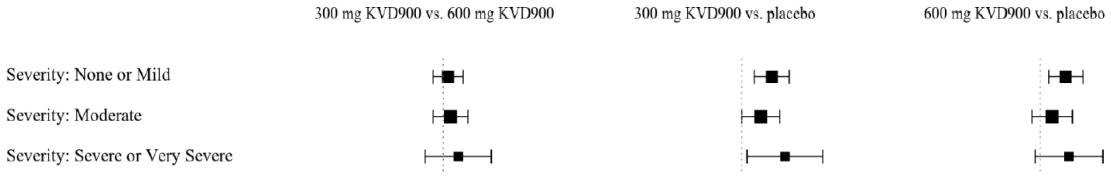


On demand and prophylaxis sub-groups: there were significant differences between patients on sebetralstat and those on placebo, whether they were in the on-demand subgroup or the prophylaxis subgroup. But in case of sub-group under kallikrein treatment no significant difference can be statistically defined due to the under-representativeness of patients in this sub-group (please see also question 179).

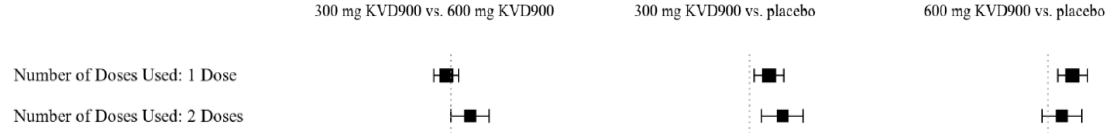


Type HAE: in the same way, there were significant differences between patients taking sebetralstat (300 mg or 600 mg) and those taking placebo, regardless of whether they had type I or type 2 HAE.

Severity of seizures: Regarding the severity of moderate to severe seizures, both doses of sebetralstat were significantly better than placebo.



IMP dose: Finally, with regard to the number of doses of sebetralstat taken per attack, bearing in mind that these results are only for subgroups for which only the trend of the results is relevant, there appears to be a significant difference between the 300 mg and 600 mg doses with regard to the use of a second dose of sebetralstat.



The superiority of sebetralstat over placebo at doses of 300 mg and 600 mg is clearly demonstrated for both the primary and secondary endpoints. Moreover, it is not really possible to distinguish between the efficacy of both two doses of sebetralstat, 300 mg or 600 mg. But it is not excluded that in a more discriminant patient subgroup such as the severe patients with laryngeal attack the likelihood of response would be higher with 600 mg but this could not be ascertained.

SUBGROUP ANALYSES OF THE EFFICACY ENDPOINTS

Time to the second IMP administration within 12 hours and 24 hours.

The number of attacks with first incidence of second IMP administration within 12 and 24 hours was lower in the 300 mg KVD900 group (26 [29.9%] patients within 12 hours and 29 [33.3%] patients within 24 hours) and 600 mg KVD900 group (35 [37.6%] patients within 12 hours and 36 [38.7%] patients within 24 hours) compared to placebo (41 [48.8%] patients within 12 hours and 42 [50.0%] patients within 24 hours).

Patients who entered the study on on-demand versus long-term prophylactic treatment

Table 7. Kaplan-Meier Estimates For the Key Primary And Secondary Endpoints By Subgroup Analysis (Full Analysis Set)

Subgroup	300 mg KVD900				600 mg KVD900				Placebo		
Endpoint	n	No. of patients Events n (%)[a]	Median (95% CI)	Nominal p-value*	n	No. of patients Events n (%)[a]	Median (95% CI)	Nominal p-value*	n	No. of patients Events n (%)[a]	Median (95% CI)
Prophylactic treatment status: On prophylactic treatment (Prophylaxis-FAS)											
Time to beginning of symptom relief within 12 hours	19	15 (78.9%)	1.85 (0.79, 3.47)	0.0494	21	17 (81%)	2.03(0.78, 3.41)	0.1096	18	13 (72.2%)	4.71 (2.28, 8.30)
Time to reduction in severity within 12 hours		11 (57.9%)	9.27 (1.79, NE)	0.2596		10 (47.6%)	5.53 (2.27, NE)	0.4154		8 (44.4%)	NE (5.57, NE)
Time to complete attack resolution within 24 hours		12 (63.2%)	17.05 (10.55 ,NE)	0.5654		12 (57.1%)	19.24 (5.03, NE)	0.6918		11 (61.1%)	16.49 (7.46, NE)
Prophylactic treatment status: On-demand (On-demand FAS)											
Time to beginning of symptom relief within 12 hours	68	51 (75.0%)	1.35 (0.98, 1.83)	<0.0001	72	54 (75.0%)	1.77 (1.31, 2.27)	0.0025	66	28 (42.4%)	NE (2.04, NE)
Time to reduction in severity within 12 hours		33 (48.5)	8.45 (3.40, NE)	0.0029		39 (54.2)	8.15 (2.79, NE)	0.0025		18 (27.3)	NE (NE, NE)
Time to complete attack resolution within 24 hours		25 (36.8)	NE (22.90, NE)	0.0007		34 (47.2)	NE (10.52, NE)	<0.0001		12 (18.2)	NE (NE, NE)

Table 6-8 Kaplan-Meier Estimates For The Key Primary And Secondary Endpoints By Subgroup Analysis (Full Analysis Set)

Subgroup	300 mg KVD900	600 mg KVD900	Placebo

The applicant should discuss whether patients who entered the study on on-demand versus long-term prophylactic treatment presented with different baseline characteristics of HAE attacks (severity, localisation). In the response document the applicant has analysed the results as requested above by treatment use (on-demand only, any long-term prophylaxis (LTP), kallikrein prophylaxis (including lanadelumab and berotralstat) and other prophylaxis). In addition, the sponsor conducted an additional subgroup analysis to examine efficacy by treatment use and baseline attack severity (none or mild, moderate, severe or very severe), primary attack location (neck or above, abdomen, other), or age (<18, >=18). These results are for

information only, given the small numbers in each subgroup. However, we agree with the sponsor that they could support the efficacy of sebetralstat versus placebo for patients who entered the study on on-demand versus long-term prophylactic treatment.

- **Ancillary analyses**

N/A

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8. Summary of Efficacy for Trial

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)		
Study identifier	2021-001226-21	
Design	**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 was designed to stop once a specified number of attacks were captured. At that point on-going patients would be terminated.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	23-02-2022 to 31-12-2023 = 93 weeks not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Patients were to self-administer a single oral dose of - 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), - 600 mg KVD900 (2 × 300 mg KVD900 tablets), - or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP could be administered for each attack. The Treatment Period will begin when the first HAE eligible attack occurs. Patients will treat 3 separate, eligible HAE attacks with their assigned IMP treatment for that attack	
Endpoints and definitions	**Primary End Point** The 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	Difference in median time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration.
	Secondary End Point N°1 The PGI-S: Time to first incidence of decrease from baseline for two time points in a row within 12 hours of the first IMP administration.	Difference in median time to first incidence of decreases from baseline for 2 time points in a row in PGI-S within 12 hours of the first IMP administration.

	Secondary End Point N°2 The PGI-S: Time to HAE attack resolution defined as "none" on PGI-S within 24 hours of the first IMP administration without conventional attack treatment use.	Difference in median time to first incidence of complete attack resolution from baseline for 2 time points in a row in PGI-S within 24 hours of the first IMP administration.
Database lock	31 January 2024	

Results and Analysis

Analysis description	**Primary Analysis / Time to beginning of symptom relief**			
Analysis population and time point description	Full Analysis Set: The FAS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses. A total of 110 patients treated at least 1 attack with IMP and were therefore included in FAS and the Safety Set. All 110 patients treated their first attack with IMP, 86 patients treated also their second attack with IMP, and 68 patients also treated their third attack with IMP, for a total of **264 treated attacks.**			
Descriptive statistics and estimate variability	Treatment group	300 mg	600 mg	Placebo
	Number of treated attacks **264 attacks in total**	87	93	84
	Time to Beginning of Symptom Relief on PGI-C within 12 Hours (Full Analysis Set)	1.61	1.79	6.72
	Median (95% CI)	(1.28, 2.27)	(1.33, 2.27)	(2.33, NE) NE >12 hours
Effect estimate per comparison	There was a statistically significant faster time to the beginning of symptom relief for 300 mg of sebetralstat (Bonferroni adjusted $p < 0.0001$) and 600 mg of sebetralstat (Bonferroni adjusted $p < 0.0013$) compared to placebo			
Analysis description	**Key Secondary 1 Objective / Time to reduction in severity**			
Effect estimate per comparison	There was a statistically significant faster time to reduction in severity for 300 mg of sebetralstat (Bonferroni adjusted $p = 0.0036$) and 600 mg of sebetralstat (Bonferroni adjusted $p = 0.0032$) compared to placebo			
Analysis description	**Key Secondary 2 Objective / Time to complete attack resolution**			
	There was a statistically significant faster time to complete attack resolution for 300 mg of sebetralstat (Bonferroni adjusted $p = 0.0022$) and 600 mg of sebetralstat (Bonferroni adjusted $p < 0.0001$) compared to placebo.			

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Number of patients in controlled Trials	5	0	0
Number of patients in non-controlled Trials	0	0	0

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analyses of the two double-blind, placebo-controlled efficacy studies (KVD900 201 Part 2 and KVD900-301) have been performed.

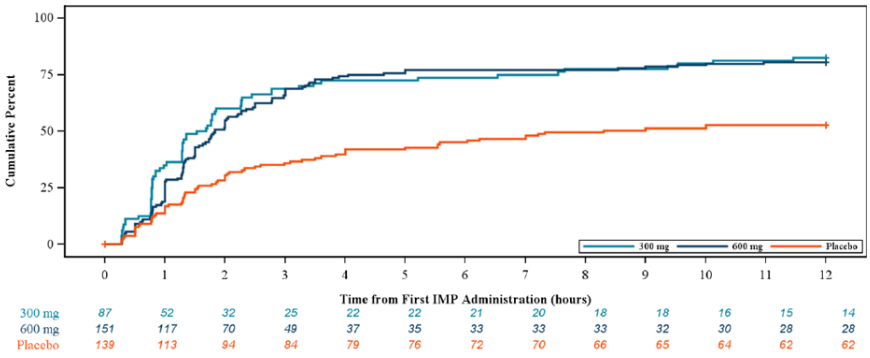
A total of 170 patients were enrolled in the double-blind, placebo-controlled efficacy trials (60 patients in KVD900-201 Part 2 and 110 patients in KVD900-301), of whom 121 patients (71.2%) completed their respective trial. As these are event-driven trials, the trials were designed to stop once a pre-specified 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, and patients were allowed to roll over into KVD900-302. Accordingly, the most frequently reported reason for discontinuation was this pre-specified termination of trials by the sponsor (39 patients [22.9% of total enrolled]).

Demographic and Baseline Characteristics

Overall, based on pooled analyses, mean (SD) age was 38.0 years (14.43) (range: 13 to 74 years). Thirteen adolescents aged ≥12 to <18 years were evaluable for the primary analysis and included (all from KVD900-301). The majority of patients were female (57.1%). The majority of patients were white (89.4%). Mean (SD) BMI at baseline was 27.37 (5.98) kg/m2. Overall, demographic and baseline characteristics were generally balanced between patients in KVD900-201 Part 2 and KVD900-301, with the exception of differences due to trial design (e.g. adolescents were not enrolled in KVD900-201). In KVD900-301, 101 of 110 patients (91.8%) had HAE type 1 and 9 patients (8.2%) had HAE type 2. In KVD900-201, HAE type was not collected. In KVD900-301, 24 patients (21.8%) entered the trial using stable long-term prophylactic treatment (including berotralstat, lanadelumab, and C1-INH) while 86 patients (78.2%) were using only on-demand treatment for HAE. In KVD900 201, all patients entered the trial using on demand treatment only per trial design.

Across all dose groups, all severity levels were reported at the time of treatment, including mild, moderate, severe, and very severe. The largest proportion of attacks were rated as mild (45.1%); 40.6% of attacks were rated as moderate, 10.3% of attacks were rated as severe, and 2.4% of attacks were rated as very severe. Note: only mild and moderate attacks (based on PGI S category) were eligible for treatment with IMP in KVD900-201 per protocol; in KVD900 301, any severity level was eligible (with the exception of severe laryngeal attacks, which were excluded). Across all dose groups, the most commonly reported baseline anatomic locations were abdomen (39.8%), arms/hands (36.1%), and legs/feet (31.6%).

Results

Results and Analysis				
Analysis description	**Primary Analysis / Time to beginning of symptom relief**			
Analysis population and time point description	Full Analysis Set: The FAS included all randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. If one or more patient(s) received the incorrect trial medication, data summarised using the FAS were presented according to the randomised treatment. The FAS was the population for efficacy analyses. A total of 377 attacks were treated and included in the FAS, of which 87 in the 300 mg KVD900 group, 151 in the 600 mg group, and 139 in the placebo group.			
Descriptive statistics and estimate variability	Treatment group	300 mg	600 mg	Placebo
	Number of treated attacks **377 attacks in total**	87	151	139
	Time to Beginning of Symptom Relief on PGI-C within 12 Hours (Full Analysis Set)	1.61	1.83	8.30
	Median (95% CI)	(1.28, 2.27)	(1.50, 2.27)	(4.00, NE) NE >12 hours
Effect estimate per comparison	Time to beginning of symptom relief was faster for attacks treated with both sebetralstat 300 mg (nominal p=0.0001) and 600 mg (nominal p<0.0001) compared with placebo.  **Figure 6. Kaplan-Meier Plot for Time to Beginning of Symptom Relief within 12 Hours of Initial IMP Administration (ISE Full Analysis Set)**			

Analysis description	Key Secondary 1 Objective / Time to reduction in severity
Effect estimate per comparison	Time to reduction in severity was faster for attacks treated with both sebetralstat 300 mg (nominal p=0.0041) and 600 mg (nominal p<0.0001) compared with placebo.

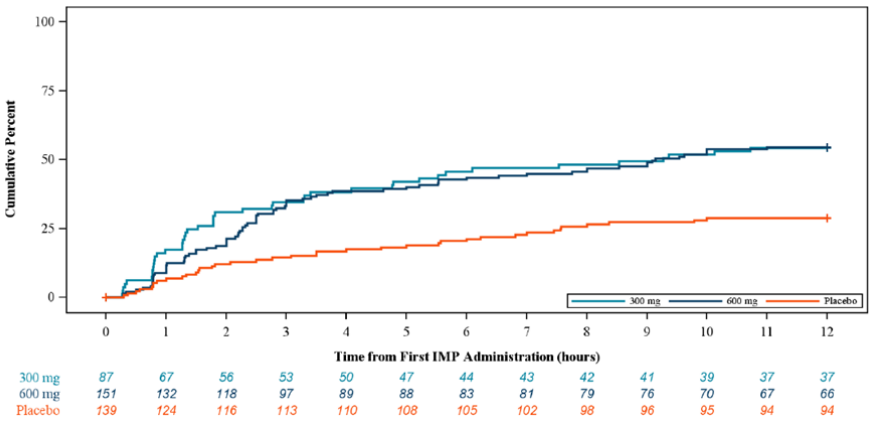


Figure 7. Kaplan-Meier Plot for Time to Reduction in Severity within 12 Hours of Initial IMP Administration (ISE Full Analysis Set)

Analysis description	Key Secondary 2 Objective / Time to complete attack resolution
Effect estimate per comparison	Time to complete attack resolution was faster for attacks treated with both sebetralstat 300 mg (nominal p=0.0021) and 600 mg (nominal p<0.0001) compared with placebo.

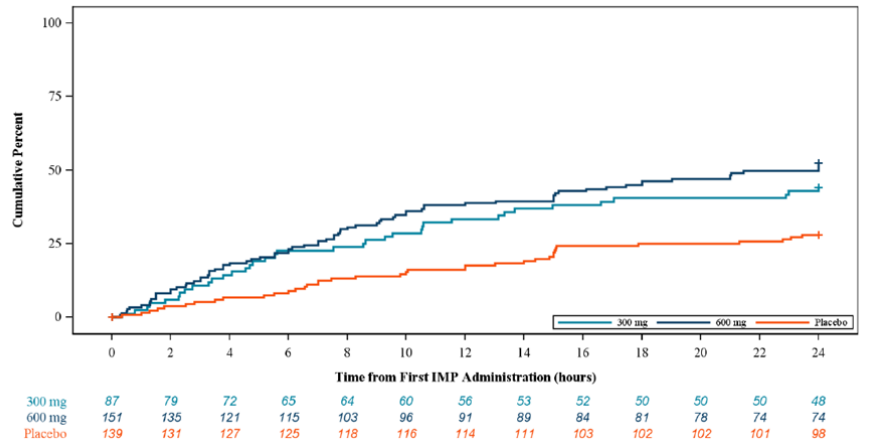


Figure 8. Kaplan-Meier Plot for Time to Complete Attack Resolution within 24 Hours of Initial IMP Administration (ISE Full Analysis Set)

2.6.5.6. Supportive study

Study Phase 2 - KVD900-201

This is a phase 2 randomised, two-part, two-sequence, two-period (2 x 2) crossover clinical trial. The aim of the KVD900-201 trial was to evaluate the efficacy, safety, and tolerability of a single administration of sebetralstat 600 mg (i.e. 2 fold the claimed 300 mg dose) compared with placebo in halting the progression of a peripheral or abdominal attack in adult patients with HAE type 1 or2.

- in part I, to investigate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of sebetralstat 600 mg during the intercritical period between HAE attacks.

- in part II, following randomisation 1:1, to assess 2 sequences: either a single administration of sebetralstat 600 mg to treat the first eligible HAE attack within 1 hour of start of attack, and following resolution of this attack, a second single administration of placebo to treat the second eligible HAE attack, or the placebo administration first, followed by the sebetralstat secondly.

If a subject received conventional attack treatments, such as C1-INH or icatibant (all doses), the following washout periods were required prior to the subsequent dosing with the study drug: 7-day washout period required for C1INH; 3-day washout period required for icatibant.

In this double-blind, randomised, placebo-controlled, crossover trial, the primary endpoint, time to use of conventional attack treatment within 12 hours of the IMP, was met with statistical significance (p=0.010). Following treatment with sebetralstat, the proportion of patients in the FAS used conventional attack treatment within 12 hours was halved with IMP (8/53 patients [15.1%]) as compared to those treated with placebo (16/53 patients [30.2%]). All secondary endpoints met p values of <0.05 demonstrating the efficacy of 600 mg of sebetralstat against placebo. The primary and secondary efficacy endpoints are based on different scales (tools) of assessment by the patients. These tools are called the PRO (Patient Reported Outcome).

Following treatment with sebetralstat, the following was observed:

- Lower proportion of attacks that worsened on PGI-S over a 12-hour period following treatment: 11/53 subjects [20.8%] in comparison to following treatment with placebo (24/53 subjects [45.3%]).
- Higher proportion of attacks defined as "a little better" or higher on PGI-C for 2 consecutive time points within 12 hours of study drug : 44/53 subjects [83.0%] in comparison to following treatment with placebo (27/53 subject [50.9%]).
- In addition 600 mg KVD900 was found to bring relief from an attack of HAE with the following outcomes on the PGI-C / Patient Global Impression of Change (1.6 hours versus 9 hours, KVD900 versus placebo), PGI-S / Patient Global Impression of Severity (9.0 hours versus > 24 hours, KVD900 versus placebo), and the composite VAS / Median time to symptom relief (6 hours versus 19 hours, KVD900 versus placebo).

KVD900-302 is an Open-Label Extension Trial to Evaluate the Long-term Safety of KVD900, for On-demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema type 1 or 2 (KONFIDENT-S).

The Primary objective is to assess the safety of long-term administration of KVD900 in adolescent and adult patients with hereditary angioedema (HAE) type 1 or 2. The secondary objective is to assess the long-term efficacy of KVD900 in the treatment of attacks in adolescent and adult patients with HAE type 1 or 2.

2.6.6. Discussion on clinical efficacy

In support of the application the applicant submitted one pivotal Phase 3, double-blind, randomised, crossover, placebo-controlled efficacy trial in adult and paediatric patients aged 12 years and older with HAE type 1 or 2 (KVD900-301) (sebetralstat 300 mg and 600 mg) with supportive data from a Phase 2 double-blind, randomised, crossover, placebo-controlled efficacy and safety trial in adult patients with hereditary angioedema (HAE) type 1 or 2 (KVD900-201) (sebetralstat 600 mg), and an ongoing Phase 3 open-label safety trial of long-term use of 600 mg sebetralstat in adult and paediatric patients aged 12 years and older with HAE type 1 or 2 (KVD900-302).

Phase 1 studies

Although a formal dose proportionality study was not conducted, data from both KVD900-101 and KVD900-110 as well as a PK modelling report, support that the PK between the 300 mg and 600 mg doses are proportional.

Phase 2 study

It is noted that this study validated the patient reporting methods for the primary and secondary endpoints and demonstrated the efficacy of 600 mg KVD900 versus placebo in adult patients suffering from HAE attacks.

However, the Phase 2 study, KVD900-201, was an event-driven trial, which means the trial was designed to stop once a pre-specified number of evaluable attacks was treated with IMP. As a result, of the total of 68 patients who completed Part 1 of KVD900 201, and randomised in Part 2, 15 (22.1%) patients were withdrawn from the trial early, with the majority of patients withdrawn from the trial due to primary reason "Other (early discontinuation per protocol; sufficient number of patients completed the trial)" (13/68 patients [19.1%]). The phase 2 primary efficacy population only included patients completing both periods (due to the planned statistical test), so that the number of attacks was directly linked to the number of patients completing the trial. The applicant designed the trial estimating that 50 patients completing both treatment arms would provide adequate power to address the objectives of the trial. As this was an event-driven trial, it was not possible to track in real-time when the 50th patient would treat their second attack. As soon as confirmation that the 50th patient completed their 2nd treatment arm, trial sites were notified to schedule end-of-trial (EOT) visits with any patients that were ongoing. Patients were allowed to continue to treat attacks with Investigational Medicinal Product (IMP) until their final visit occurred. This resulted in a total of 53 patients who completed both treatment arms and were included in the FAS for the phase 2 trial. Several patients only completed one treatment arm and were not included in the primary analysis.

Having in mind that in this study the efficacy was a secondary objective and that the 600 mg but not the to-be-marketed 300 mg was tested, this study was only regarded as supportive and mostly for safety purpose.

Dose selection for the pivotal study

No real dose-ranging efficacy study was conducted prior to the pivotal KVD900-301 study, although it was pointed out in the Scientific advice. Furthermore, the applicant did not justify with other PK/PD data, why the 300 mg dose was finally chosen, in addition to the 600 mg dose, for the phase 3 pivotal study design, while the phase 2 study results were clinically significant with the 600mg dose. Nevertheless, this issue is considered resolved given that the benefit/risk was deemed acceptable at the applicant's claimed 300 mg dose.

Pivotal KVD900-301 (KONFIDENT) study

Study design

The use of a placebo was agreed during the scientific advice.

Patients were to be treated as soon as possible after recognition of the start of the attack. Patients treated each attack with up to 2 of doses IMP, administered at least 3 hours apart. Eligible attacks were to be treated with a single administration of IMP.

In study KVD900-301 at least 48 hours (i.e. washout period) must have elapsed since patient has used conventional on-demand treatment or IMP to treat an HAE attack. This is found acceptable.

Given the rarity of the condition, a single pivotal trial was considered acceptable to CHMP at the time of scientific advice, "provided that results are compelling, robust and taking into account the internal and external validity, clinical relevance, data quality and internal consistency", as per EMA guidance (CPMP/EWP/2330/99). The cross-over design was also found acceptable to reduce sample size and inter-individual variability, which seemed reasonable in this rare disease.

The description of the pivotal phase 3 study was difficult to interpret. Indeed, the protocol (v4, 26 April 2023) states that approximately 114 patients were to be randomised to ensure that approximately 84 patients (including 12 adolescents) completed the trial. However, 136 patients were actually randomised and only 68 patients completed the trial. According to the study report, the trial stopped "once a specified number of attacks were captured". The applicant recognised that several terms (patients, completers and attacks) were unfortunately used interchangeably in the study protocol and statistical analysis plan. It appears that the phase 3 study protocol and SAP were written in a similar manner as for the previous phase 2 trial, without sufficiently considering important differences in study design and analysis. It is agreed that based on the study design and analysis of study KVD900-301, the number of attacks assigned to each study treatment is the main driver of study power (rather than the number of patients, or the number of completers). Following clarifications, it is found acceptable that the sample size determination and the trial stopping rule were based on the number of attacks to be treated per treatment arm (i.e. 84 attacks per study treatment).

The randomisation procedure itself, i.e. with patients receiving 3 treatments in randomised crossover fashion based on their assignment to 1 of the 6 treatment sequences is acceptable. The stratification by whether the patient enters the trial taking only on-demand vs prophylactic treatment was also relevant and supported during scientific advice.

The primary analysis was the FAS which included randomised patients who received trial medication from at least one period for the respective qualifying HAE attack. As a consequence, not all randomised patients were included in efficacy analyses, as some did not have any HAE attack treated with trial medication following randomisation (26 out of 136 randomised patients). This is due to the dissociation, per study design, between randomisation and treatment. Moreover, a large proportion of randomised patients did not complete their full treatment sequence, mostly due to the trial terminating after having reached a targeted number of events. In other words, the randomisation is not preserved in the data set that is effectively used for analyses, and potential imbalances in disease characteristics across study treatments at the time of HAE attacks could possibly lead to biased estimates of treatment effect. Nevertheless, it is acknowledged that the applicant provided demographic, disease characteristics and medical history in the FAS by randomised treatment sequence, as well as a summary of baseline characteristics of HAE Attacks by study treatment. These summaries allowed assessment of any imbalances induced by the non-preservation of the full randomisation sequences.

The applicant justifies the absence of carryover effect by the short half-life of sebetralstat, by subjects being instructed to use study drug at least 48 hours from the previous attack, and by the actual durations between attacks within a subject being substantially longer than 48 hours. In addition, some requested analyses of primary and key secondary endpoints and by order of the treated HAE attack generally support the absence of carryover.

Although the rationale for using a composite strategy for the administration of conventional attack treatment is understood (conventional attack treatment prior to symptom relief may be considered as treatment failure), it was of interest to further investigate the effect of treatment under a different strategy that would reflect clinical practice. For that purpose, the applicant provided a supplementary analysis of primary and key secondary endpoints when making use of available data following the administration of conventional attack treatments (i.e. following a treatment policy strategy for this ICE). Overall, the results remained consistent with the primary and key secondary analyses.

The ICE of study discontinuation is handled using a hypothetical strategy, meaning that patients are censored at time of discontinuation. This is in effect assuming censoring at random for patients who discontinued the trial prior to completing the assessment of their HAE attack under current IMP treatment. This assumption may be questionable, particularly for patients who discontinued the trial for a reason directly related to study drug or any HAE attack-related outcome. The applicant performed sensitivity analyses with imputation under informative censoring, which provide some relevant assessment of potential deviations from the main hypothetical strategy. They are currently difficult to fully interpret without an understanding of the proportion of patients censored due to study discontinuation, and the applicant was asked to provide a summary of censoring categories and associated frequencies. During the review process it was deemed that the censoring due to extensive measurements was not negligible (around 8-10% for the primary endpoint), but there was no clear pattern observed, with similar proportions of missing measurements between treatment arms.

The statistical analysis methods are themselves deemed acceptable and were supported during scientific advice. A Bonferroni multiplicity adjustment procedure was implemented to control the type I error across study treatment comparisons for primary and key secondary endpoints, which is acceptable.

Although the Gehan's generalised Wilcoxon test sensitivity analysis provides some consistency assessment under an alternative method, it should be noted that such analysis requires complete 2x2 sequences per patient (for each pair of treatments being compared). The number of attacks included in these sensitivity analyses is therefore reduced compared to the primary analysis on the FAS, and it would therefore be challenging to interpret inconsistent differences in treatment effects.

Several modifications to the planned analyses in the initial study protocol and SAP were made. The applicant provided a supplementary analysis of primary and key secondary endpoints when making use of available data following the administration of conventional attack treatments (i.e. following a treatment policy strategy for this ICE). Overall, the results remained consistent with the primary and key secondary analyses.

The inclusion and exclusion criteria are globally considered appropriate in line with the EMA/SA. Nevertheless, concerning "Inclusion criteria" in the EMA/SA the applicant was asked to justify the inclusion of patients on prophylactic treatment with other kallikrein inhibitors (i.e., berotralstat or lanadelumab). Indeed, it could be expected that patients on prophylactic treatment with a kallikrein inhibitor and who develop an HAE attack may have limited efficacy if treated with a product with the same mechanism of action. In the response documentation, a discussion on the potential for drug interactions between berotralstat and sebetralstat is provided, considering berotralstat as both a precipitant and object of CYP3A4-based potential DDIs. The applicant's conclusion is that sebetralstat is considered unlikely to cause any clinically significant CYP-

mediated effect on the pharmacokinetics of co-administered berotralstat. The effect of berotralstat on the CYP-mediated pharmacokinetics of sebetralstat would be consistent with its being a moderate CYP3A4 inhibitor, and therefore no dose adjustment of sebetralstat when taken with berotralstat is proposed. This is supported.

Inclusion criteria specify that if a patient "was a completer of the KVD824-201 trial within 3 months prior to randomisation and met all other entry criteria" they can enrol in KVD900-301. There is a risk that a positive selection due to efficacy as well as tolerability may result in (favourable) bias of the pivotal trial. The applicant clarified that in KVD824-201 a different compound (KVD824) than the KVD900 was used and that it was a prophylactic treatment for the prevention of HAE attacks. As eligibility criteria were stricter for the KVD824-201 trial, than for the KVD900-301 trial, patients included in KVD824-201 trial could be included in the KVD900-301 trial. Only 3 patients (each from a different clinic) that received IMP in the KVD824-201 trial were randomised and included in the KVD900-301 FAS. It is agreed that as this was a small sample size no subgroup analysis could be completed. However, the applicant did not discuss any possibility of carry-over of KVD824 in the results obtained in the Konfident study but considering this concerns only 3 patients, the potential bias is removed.

As for the phase 2, the primary and secondary efficacy endpoints are based on different scales (tools) of assessment by the patients. These tools are called the PRO (Patient Reported Outcome).

The primary endpoint for the pivotal trial was based on the PGI-C scale (Patient Global Impression of Change), a 7 points rating scale from "much worse" to "much better". This scale was considered appropriate. Other outcomes have been evaluated in other drugs or therapies for HAE. Secondary endpoints were based on PGI-S scale (Patient Global Impression of Severity). Others efficacy assessment are anxiety level assessed on the Modified GA-NRS (General Anxiety Numeric Rating Scale), 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.

During the scientific advice regarding the primary endpoint, it was suggested to use a rating of at least 'better' on a PGI-C scale as a more appropriate measure of improvement of symptoms. Following a successful outcome of the KVD900-201 trial, and utilising input from physicians and patients, a rating of "a little better" on the PGI-C was selected as the most effective at capturing the beginning of symptom relief earlier than other measures for primary efficacy endpoint and was associated with achieving "Better" or higher 85% of the time within the assessment period. This is considered acceptable.

Selection of study population

This trial was conducted at 66 sites worldwide: in Europe, North America and Asia/other.

The patient population were adults and adolescents aged 12 years and older diagnosed with either type 1 or type 2 HAE (excluding any other form of angioedema) with at least 2 documented HAE attacks within 3 months prior to screening or randomisation.

Patients using long-term prophylactic treatment were allowed to participate if they had been on a stable dose and regimen for at least 3 months prior to the screening visit (and for the duration of the trial). In accordance with the exclusion criteria, [patients who used ACE-inhibitors, oestrogen-containing medications with systemic absorption, strong cytochrome P450 3A4 inhibitors or inducers]; [patients who were pregnant or breastfeeding]; [patients with hepatic impairment defined as a Child-Pugh B or C]; [patients participating in KVD900-201 trial and any interventional investigational clinical trial (with the exception of KVD824-201) within 4 weeks of the last dosing of investigational drug prior to screening] were excluded from participation

in KVD900-301 trial. In the response document the applicant discussed the inclusion of patients under prophylactic treatment with other C1-INH (in particular berotralstat and lanadelumab), reflecting on potentially shared mechanism of action and possible impacts on efficacy (please see section 3.3.1). A response document is also provided regarding patients with different levels of hepatic impairment (see section 2.6.2 clinical pharmacology).

Eligible HAE attacks

Eligible HAE attacks for treatment with IMP must have met the following criteria: patient must have been able to identify the start time of the attack, at least 48 hours must have elapsed since patient has used conventional on-demand treatment or IMP to treat an HAE attack, patient must be have been able to complete at least the first 4 hours of diary assessments following the first administration of IMP, and post-attack televisit must have been completed for the previous eligible attack (applicable to eligible attacks 2 and 3 only).

In regard to attack severity, patients experiencing severe laryngeal attacks were not eligible for treatment. This is considered appropriate from a medical emergency point of view, as well as inability to administer a product formulated as a tablet in this situation.

Considering that, apart from the washout period for the IMP administration, no minimal time interval was set between two eligible HAE attacks, the applicant provided the median (95% CI) time interval between the first and second attack and the median (95% CI) time interval between the second and third attack. All median time intervals and their lower confidence limits exceeded the 48-hour observation period used in the KONFIDENT KVD900-301 trial, as well as the typical duration of an HAE attack (normally 2–5 days). Therefore, it can be concluded that a new attack cannot be an exacerbation of the previous one.

Trial interventions

Patients were to self-administer a single oral dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 600 mg KVD900 (2 × 300 mg KVD900 tablets), or 2 matching placebo tablets as soon as possible after recognition of the start of the attack. If needed (as determined by the patient), after at least 3 hours a second dose of IMP could be administered for each attack. If symptoms progressed to or included airway involvement (laryngeal attacks), patients were allowed to take conventional on-demand treatment at any time.

As per dosing recommendations in the SmPC, a second 300 mg dose could be taken, if needed. A dosing interval for the second 300 mg dose, has been recommended and implemented in the SmPC, section 4.2 corresponding to the conditions of clinical trial KONFIDENT KVD900-301, i.e. respecting a time period of 3 hours before taking a second 300 mg dose. Further, it is also recommended that no more than two 300 mg doses should be taken within 24 hours.

Efficacy results – pivotal study KVD900-301

PATIENT DISPOSITION

136 patients were randomly assigned to receive the IMP, of which a total of 110 patients treated at least 1 attack with IMP and were therefore included in FAS and in the Safety set analysis. All of 110 patients treated their first attack with IMP, 86 patients treated also their second attack with IMP, and 68 patients also treated their third attack with IMP, for a total of 264 treated attacks, meaning only 68 patients treated all 3 attacks with the IMP. Only 68 of the 110 patients completed the trial (i.e. due to targeted number of attacks reached) and 42 patients (38.2%) were discontinued from the trial. The primary reason for trial

discontinuation was that the specified number of attacks for trial completion was reached and ongoing patients were terminated (32/110, 29.1% of patients). This was recorded as trial termination by sponsor in the EDC. For the remaining 10 patients that discontinued from the trial, the reasons stated were: withdrawal by patient (3), other reasons (3), lost to follow up (2), protocol violation (1) and withdrawn due to physician decision (1).

In regard to patient disposition by sequence, the highest completion rate was in sequence B (placebo →KVD900 300 mg→KVD900 600 mg) with 14/18 (77.8%) of patients completing the trial and 4/18 (22.2%) of patients being censored, of which 2 being right censored following trial termination by sponsor. The lowest completion rate was in sequence E (KVD900 600mg→KVD900 300mg→placebo) with 8/20 (40%) of patients completing the trial and 12/20 (60%) of patients being censored, of which 11 right censored following trial termination by sponsor. The applicant explained that if the completion rates differ significantly between the sequences, this is the consequence of 'Trial terminated by sponsor'. As this was an event-driven study, the study team took the decision to stop the study when the target number of attacks treated with the IMP (252 attacks) was approached. This is agreed that the observed differences were not related to bias in the conduct or interpretation of the data and had no impact on the efficacy results.

PROTOCOL DEVIATIONS

Major protocol deviations were reported for 17.6% (24/136) of randomised subjects. Most of the events reported were in regard to no consecutive assessment completed before the first 12 hours and no conventional medication taken (9.6%, 13/136 subjects), not taking the full dose per protocol requirements (2.9%, 4/136 subjects) and taking conventional medication within 48 hours prior to the IMP (2.9%, 4/136 patients). Additionally, 2 protocol deviations were added to the clinical trial management system post-database lock: 2 patients did not return unused IMP at the study visit and pills accountability could not be performed.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

On-demand therapy and long-term prophylaxis (LTP) patients

For more accurate analysis, the treatments used (on demand, prophylactic, berotralstat, lanadelumab, others) according to the profile of the HAE disease (severity, localisation, age) were requested. A total of 86 patients (78.2%) receiving on-demand only therapy reported 383 attacks, while 19 patients out of 24 patients (21.8%) on kallikrein long-term prophylaxis (LTP), including lanadelumab and berotralstat, reported 73 attacks. Additionally, 5 patients on other forms of LTP reported a total of 26 attacks. The small number of patients and attacks in the "other LTP" group was insufficient to allow for meaningful comparisons with the other two categories.

The characteristics of the hereditary angioedema (HAE) attacks were generally comparable between groups in terms of maximum severity. Most HAE attacks were classified as either moderate (49.2% for on-demand therapy vs. 52.1% for kallikrein LTP) or mild (31.4% for on-demand therapy vs. 39.7% for kallikrein LTP).

Regarding the location of HAE attacks, minor differences were observed between the on-demand treatment group and the kallikrein LTP group. Abdominal attacks were the most common in both groups, accounting for 49.5% in the on-demand group and 46.6% in the LTP group. Notably, a higher proportion of attacks affected arms/hands in the on-demand group compared to the LTP group (34.0% vs. 6.8%, respectively). Conversely, attacks involving head/face/neck were more frequent in the kallikrein LTP group than in the on-demand group (28.8% vs. 9.3%, respectively). The proportion of attacks involving the larynx or throat was low across all observed groups, accounting for 2.3% in the on-demand group, 5.5% in the kallikrein LTP group, and

none (0%) in the other LTP group. Hereditary angioedema attacks involving other locations were reported in similar proportions across the observed groups.

In conclusion, the baseline characteristics of HAE attacks (severity, location) showed data were largely comparable between patients who entered the study on on-demand treatment and those on long-term prophylaxis.

Baseline characteristics of the IMP-treated HAE attacks

A total of 264 attacks were treated and included in the FAS, of which 87 in the 300 mg KVD900 group, 93 in the 600 mg group, and 84 in the placebo group. The majority of the attacks were of mild (113 [42.8%]) or moderate (102 [38.6%]) severity on the PGI-S at the time of treatment. Thirty-eight (14.4%) attacks were severe and 7 (2.7%) were very severe. The majority of primary pooled attack locations were subcutaneous only 142 (53.8%) and abdominal only 85 (32.2%). The laryngeal swelling occurred in 8 (3.0%) of the attacks.

in Study KVD900-301, a total of eight attacks involving the larynx (3%) were reported: two in the group treated with 300 mg, two in the group treated with 600 mg, and four in the placebo group. The results from the open-label KVD900-302 trial with the 14 September 2024 data cutoff were presented which included the data on 32 attacks involving the larynx. The data were comparable to the results for the primary and key secondary endpoints for the HAE population studied in the KVD900-301 trial. The overall median time from onset of attack to first IMP administration in study KVD900-301 was 41 minutes (range: 6.0 to 140). In study KVD900-302, the median (IQR) time to treatment was 11.5min (1.0-34.0) for laryngeal attacks and 20.0 minutes (1.0, 61.0) for abdominal attacks.

Baseline characteristics for IMP-treated attacks were similar across the treatment groups.

PRIMARY 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.

Regarding the primary endpoint, there was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg KVD900 versus placebo group (and between 600 mg KVD900 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.

According to the Gehan score transformation test for FAS, these results can be considered statistically significant, with adjusted $p<0.0001$ for the comparison between 300 mg KVD900 and placebo, and adjusted $p=0.0013$ for the comparison between 600 mg KVD900 and placebo.

Furthermore, these results can be considered clinically relevant since the time to beginning of symptom relief with both doses of sebetralstat is reduced of about 5 hours compared to the placebo, which is satisfactory. Moreover, the number of attacks relieved is increased with both doses of sebetralstat of about 25% compared to the placebo, which is satisfactory. [(300 mg KVD900 group: 66 [75.9%] attacks and 600 mg KVD900 group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).

Sensitivity Analysis for Primary Endpoint on FAS

Results of the sensitivity analysis was in line with the FAS results of the primary analysis, with similar size effect:

As explained above, the Gehan's generalised Wilcoxon test sensitivity analysis provides some consistency assessment under an alternative method. Such analysis requires complete 2x2 sequences per patient (for each pair of treatments being compared). The number of attacks included in these sensitivity analyses is therefore reduced compared to the primary analysis on the FAS.

Indeed, the conducted sensitivity analysis assesses 71 patients in the 300mg vs placebo group and 76 patients in the 600mg vs placebo group.

The time to beginning of symptom relief was reached faster in the 300 mg KVD900 versus placebo group (nominal p=0.007) and 600 mg KVD900 versus placebo group (nominal p<0.0001) within the 12-hour analysis window.

The median (95% CI) time to the beginning of symptom relief was 1.69 hours (95% CI: 1.28, 2.28) for 300 mg KVD900 group versus 5.57 hours (95% CI: 2.07, NE) for placebo group comparison and 2.01 hours (95% CI: 1.38, 2.46) for 600 mg KVD900 group versus 7.32 hours (95% CI: 1.38, 2.46) for placebo group comparison.

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: 55 [77.5%] attacks versus placebo group: 36 [50.7%] attacks; and 600 mg KVD900 group: 60 [78.9%] attacks versus placebo group: 37 [48.7%] attacks).

Time to the second IMP administration within 12 hours and 24 hours.

The number of attacks with first incidence of second IMP administration within 12 and 24 hours was lower in the 300 mg KVD900 group (26 [29.9%] patients within 12 hours and 29 [33.3%] patients within 24 hours) and 600 mg KVD900 group (35 [37.6%] patients within 12 hours and 36 [38.7%] patients within 24 hours) compared to placebo (41 [48.8%] patients within 12 hours and 42 [50.0%] patients within 24 hours).

KEY SECONDARY ENDPOINT 1 / TIME TO REDUCTION IN SEVERITY (PATIENT GLOBAL IMPRESSION OF SEVERITY)

PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.

Regarding the key secondary endpoint 1 on the PGI-S, 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 on the PGI-S was 9.27 hours (4.08, not evaluable [i.e. >12 hours]) for attacks treated with 300 mg, 7.75 hours (3.27, >12 hours) for attacks treated with 600 mg, and Not evaluable (>12 hours) for attacks treated with placebo.

Furthermore, 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). The baseline PGI-S score (p<0.0001), which was controlled for in the mixed model showed significant impact on time to first incidence of decrease on PGI-S.

KEY SECONDARY ENDPOINT 2 / TIME TO COMPLETE ATTACK RESOLUTION

PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration.

Regarding the key secondary endpoint 2 on the PGI-S, there was a statistically significant improvement in the time to complete HAE attack resolution within 24 hours between 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 attack resolution on the PGI-S ("none") was not evaluable (i.e. >24 hours) (16.60, >24) for attacks treated with 300 mg, 24.00 hours (10.6, >24) for attacks treated with 600 mg, and not evaluable (>24 hours) for attacks treated with placebo.

More 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).

HAZARD RATIO BETWEEN TREATMENTS FOR PRIMARY AND KEY SECONDARY ENDPOINTS

An ad-hoc proportional hazard regression was performed to compare the treatment effect on the primary and key secondary endpoints between the 300 mg and 600 mg dose levels in all subgroups studied. The results were presented and analysed by the applicant using forest plots. The superiority of sebetralstat over placebo at doses of 300 mg and 600 mg is clearly demonstrated for both the primary and secondary endpoints. Furthermore, it is not really possible to distinguish between the efficacy of the two doses of sebetralstat, 300 mg or 600 mg. However, it cannot be excluded that in a more discriminating subgroup of patients, such as those with severe laryngospasm, the likelihood of response may be higher with 600 mg, but this could not be determined.

SECONDARY ENDPOINTS

Efficacy results of sebetralstat compared to placebo in terms of superiority were consistent and supportive of the primary and key secondary endpoints across all secondary and exploratory endpoints.

SUBGROUP EFFICACY RESULTS

Assessment of paediatric data on clinical efficacy

The low number of patients (only 11 patients received the dose 600mg and 10 patients received the dose 300mg) do not allow to conclude on the primary efficacy endpoint. Across all trials involving adolescents (KVD900-301 and KVD900-302) 32 adolescents have been treated corresponding to 390 attacks. The frequency of their seizures is often lower than that of adults. This may be explained by pharmacokinetic data. The pharmacokinetic data available from the six adolescent patients in study KVD900-302 and the 14 paediatric patients in study KVD900-303 have been incorporated into a new PPK model. It appears that for the 600 mg dose, results are similar between adolescents and adults. However, for the 300 mg dose, results are higher in adolescents than in adults. The estimated C_{max} in patients ≥12 years of age and in the 20 kg – 45 kg weight group following a single 600 mg dose of sebetralstat was comparable to a single 600 mg dose in adults in the 45+ kg weight group (geomean C_{max} 5,730 ng/mL vs 5,260 ng/mL, respectively). Therefore, based on efficacy results provided in KONFIDENT KVD900-301 trial no dose adjustment in patients adolescents aged 12 years and older is necessary.

Analysis performed across trials (pooled analyses)

Pooled analyses of the two double-blind, placebo-controlled efficacy studies (KVD900 201 Part 2 and KVD900-301) have been performed.

Although the applicant's efforts to combine phase 2 (KVD900-201 trial part 2) and phase 3 (KVD900-301 trial) data in pooled efficacy analyses are appreciated, there are several methodological concerns associated to them.

First, it should be noted that the pooled analyses are not a fully pre-specified exercise, given that the first ISE SAP (v1, 30 November 2023) was written in full knowledge of the phase 2 study results and the second version (5 April 2024) was finalised after both studies had completed.

More importantly and as accurately described by the applicant, while there are similarities between the two trials (both randomised, double-blind, placebo-controlled, cross-over designs), there are also important differences between trial designs: differences in trial populations (patients 18 years or older not on prophylactic treatment in phase 2 vs patients 12 years and older in phase 3), differences in HAE attack eligibility (laryngeal or facial attacks, severe attacks not eligible in phase 2 vs severe laryngeal attacks not eligible in phase 3), differences in dosing regimen (re-dosing allowed in phase 3). This heterogeneity may question the poolability of the two trial data sets for efficacy analyses.

Moreover, patients from the phase 2 trial were eligible to enter the phase 3 study. The proportion of phase 3 patients that had previously participated to phase 2 is currently. This means that the data sets are not independent as there is an overlap of patients that subsequently enrolled in both studies. It seems from the ISE SAP that this overlap of patients and dependence between data sets has not been accounted for in the pooled statistical analyses, which might have resulted in some level of bias.

Therefore, these methodological limitations should be taken into account when reviewing and interpreting the pooled study results. Furthermore, the efficacy results presented in favour of the 300 mg and 600 mg doses versus placebo cannot be taken into account in the discussion.

Supportive study - KVD900 302 Open-Label Extension Trial - KONFIDENT-S

The applicant has submitted an Open-Label Extension Trial to Evaluate the Long-term Safety of KVD900; in Adolescent and Adult Patients with Hereditary Angioedema type 1 or 2 (KONFIDENT-S)

Considering this open label, single arm, study design with a long-term safety objective, this study is mostly supportive from a safety point of view. The efficacy is only a secondary objective.

Furthermore, the dose assessed in this study was not 300mg but 600mg. This corresponds to the highest tested dose in the 301 study, but it is not the dose claimed by the applicant in this application.

2.6.7. Conclusions on the clinical efficacy

Overall, the clinical efficacy data support the MAA of sebetralstat at a strength of 300 mg in the therapeutic *indication "Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older".*

2.6.8. Clinical safety

The clinical development program for sebetralstat has included 10 phase 1 trials, 1 phase 2 and 2 phase 3 trials. The 10 Phase 1 trials conducted in healthy subjects included PK and initial tolerability trials (KVD900-101, KVD900-102, KVD900-103), comparative bioavailability trials (KVD900 107, KVD900-108), drug-drug interaction (DDI) trials (KVD900-106, KVD900-112) and intrinsic factor PK trials, including a trial with cohorts of patients with hepatic impairment, a trial in Chinese, Japanese, and White subjects, and a thorough QT trial

(KVD900-109). The phase 2 and 3 studies include the phase 2 double-blind, crossover, placebo-controlled efficacy and safety trial in adult patients with hereditary angioedema (HAE) Type I or II (KVD900-201), the pivotal phase 3, double-blind, randomised, crossover, placebo-controlled efficacy and safety trial in adult and paediatric patients aged 12 years and older with HAE Type I or II (KVD900-301) and the ongoing phase 3 open-label safety trial of long-term use in adult and paediatric patients aged 12 years and older with HAE Type I or II (KVD900-302) (data cutoff date of 31 Jan 2024; data fully cleaned to 15 Dec 2023).

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). In the phase 2 KVD900-201 and the pivotal phase 3 efficacy trial KVD900-301, patients treated each eligible attack by 600 mg of sebetralstat or placebo (up to 2 administrations per attack) or also by 300 mg of sebetralstat in study KVD900-301. 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), and patients may also use sebetralstat as a short-term prophylactic therapy initiated prior to undergoing surgical, dental, or medical procedures. with 3 administrations of sebetralstat, each administration being approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure.

Phase 1 data were summarised by treatment groups and pooled across protocols. Among phase 1 trials, the DDI trials (KVD900-106 and KVD900-112) were pooled separately from a pool of all other phase 1 trials, due to potential confounding factor of the co administered treatments. The most relevant safety data are from the one phase 2 and two phase 3 trials since data from these trials constituted the safety profile of sebetralstat using the intended formulation within the intended patient population. Also KVD900-201 (Part 2) and KVD900-301 were controlled and allowed for direct comparison of safety profile with placebo and the open-label KVD900-302 provides long-term safety information on repeated treatment with sebetralstat.

2.6.8.1. Patient exposure

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

A total of 213 patients with HAE Type I or II have received the IMP (sebetralstat or placebo) in phase 2-3 trials up to 31 Jan 2024. Participation is ongoing for 90 patients (42.3%) 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). 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 enrol in KVD900-302 and 30 patients (14.1%) discontinued for this reason (trial termination). 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), protocol violation and physician decision (1 patient [0.5%] each).

No subjects or patients were prematurely unblinded in any trial.

As of the cut-off date for this marketing application (31 Jan 2024), the clinical program included 670 unique trial participants who received at least 1 administration of IMP (sebetralstat, placebo, and/or drug-drug interaction [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 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 total 153 healthy subjects or patients received a total of 309 exposures of 900 mg or above.

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. A total of 198 patients have treated a total of 879 attacks with sebetralstat, including 21 paediatric patients (age ≥12 to <18 years) who treated a total of 159 attacks and 5 geriatric patients (age ≥65 years) who treated a total of 27 attacks.

In Phase 3 trials, if needed (as determined by the patient), a second administration of the IMP could have been taken for each attack (KVD900-301) or within a 24-hour period (KVD900-302), noting that only a single IMP administration was allowed in KVD900-201. A total of 68 patients (31.9% of the 213 in Phase 2-3 trials) took 2 administrations of sebetralstat.

In KVD900-302, 10 of the 84 patients (11.9%) took 3 administrations of 600 mg sebetralstat (i.e. total dose 1,800 mg), for 18 attacks. In addition, 5 patients in KVD900-302 took up to 3 administrations of 600 mg sebetralstat for the purpose of short term prophylaxis.

In the Phase 2 and 3 Double-blind Safety Population, the mean (SD) number of IMP administrations received per attack was 1.3 (0.48) for patients who received 300 mg (n=86), 1.2 (0.42) for patients who received 600 mg (n=153), and 1.3 (0.45) for patients who received placebo (n=138). The majority of attacks were treated with a single administration (300 mg: 66.3%; 600 mg: 77.1%; placebo: 71.7%). In KVD900-301, a second administration was used for the remaining attacks (300 mg: 33.7%; 600 mg: 22.9%; placebo: 28.3%). Only a single administration of 600 mg sebetralstat was allowed in KVD900-201, which impacts the 600 mg and placebo data.

The median number of months for patients to be enrolled in KVD900-302 to date was 3.21 (range: 0.3 to 13.5 months). 45 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.

In the Phase 2 and 3 Double-blind Safety Population, concomitant medications for HAE were used by 32.6% to 54.3% of patients per treatment group and included both on-demand and/or prophylactic medications: lanadelumab and berotralstat (prophylaxis), icatibant (on-demand treatment), and C1-INH and conestat alfa (either prophylactic or on-demand treatment). Other concomitant medications used by ≥5.0% of patients in any treatment group were ibuprofen, paracetamol, salbutamol and metformin. In the Phase 1 Non-DDI Safety Population, concomitant medication use was as expected for the healthy subjects enrolled.

2.6.8.2. Adverse events

All TEAEs

In the Phase 1 Non-DDI Safety Population TEAEs were reported for 8 subjects (18.2%) who received <300 mg (8 total events), 1 subject (3.8%) who received 300 mg (1 event), 29 subjects (22.7%) who

received 600 mg or equivalent (50 total events), 15 subjects (17.9%) who received >600 mg (27 total events), and 10 subjects (13.5%) who received placebo (13 total events). The 95% CI for risk differences between all sebetralstat dose levels, in controlled and uncontrolled settings, versus placebo contained 0 for all categories with reported events except for IMP-related TEAEs in subjects who received sebetralstat 600 mg or equivalent (risk difference [95% CI] 18.0% [0.6, 35.4]). Further evaluation was undertaken in an ad hoc analysis that summarised 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 all categories with reported events.

In the Phase 2 and 3 studies overall, the incidence of TEAEs was similar following treatment with sebetralstat compared with placebo. In the Phase 2 and 3 Double-Blind Safety Population, 17 patients (19.8%) who received 300 mg sebetralstat reported a total of 20 TEAEs; 28 patients (18.5%) who received 600 mg sebetralstat reported a total of 39 TEAEs, and 24 patients (17.4%) who received placebo reported a total of 34 TEAEs. The 95% CI for risk differences between 300 mg or 600 mg versus placebo contained 0 for all categories with reported events.

Overall Adverse Events by Number of Exposures

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. 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 number of treatment administrations or exposures.

Frequently Reported Adverse Events

In Phase 1 studies, the only TEAE reported for ≥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 summarised 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]). Based on logical groupings of TEAE preferred terms, the grouped TEAEs observed in ≥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)

In Phase 2 and 3 studies, the type and frequency of TEAEs were similar following treatment with sebetralstat compared with placebo. The only TEAE reported by ≥ 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. Based on logical groupings of TEAE preferred terms, the grouped TEAEs observed in ≥2% of patients in any treatment group were upper respiratory tract infection (2 patients [2.3%] who received 300 mg, 2 patients (1.3%) who received 600 mg, and 6 patients [4.3%] who received placebo) and 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).

TEAEs by severity

Overall, the majority of TEAEs were mild or moderate in severity, and there were no trends between sebetralstat compared with placebo in the severity of reported events. 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) and serious event of intervertebral disc protrusion which was considered not related to IMP. In the Phase 1 Non-DDI Safety Population, all TEAEs were mild or moderate in severity.

Related TEAEs

In the Phase 1 Non-DDI Safety Population, TEAEs considered by the investigator to be related to the IMP were reported for 4 subjects (9.1%) who received <300 mg (4 total events; 3.20 events per subject-year), 1 subject (3.8%) who received 300 mg (1 event; 1.96 events per subject-year), 20 subjects (15.6%) who received 600 mg or equivalent (39 total events, 8.37 events per subject-year), 15 subjects (17.9%) who received >600 mg (25 total events; 12.50 events per subject-year), and 7 subjects (9.5%) who received placebo (10 total events; 5.68 events per subject-year). Headache was the only TEAE reported for ≥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); most of these events of headache occurred on-treatment. The risk difference (95% CI) for IMP-related TEAEs in subjects who received 600 mg or equivalent was 9.2% (-9.0, 27.5).

In the Phase 2 and 3 Double-blind Safety Population, IMP-related TEAEs were similar following treatment with sebetralstat compared with placebo. TEAEs considered related to the IMP 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. In both the Phase 2 and 3 Treated Safety Population and the Phase 3 Second administration Safety Population, there were no trends in frequency or severity of IMP-related events based on number of treatment administrations or exposures.

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

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths and other serious adverse events

No deaths occurred while on trial. Six patients reported a total of 8 treatment emergent SAEs. None were considered by the investigator to be related to the IMP. One patient (1.2%) who received 300 mg and 2 patients (1.3%) who received 600 mg reported SAEs; no SAEs were considered related to the IMP. The SAE reported for the patient who received 300 mg was Grade 3 in severity. No SAEs were reported for the Phase 1 Non-DDI Safety Population.

Other Significant Adverse Events

There were no AEs of Special Interest, and no meaningful trends were identified after review of the safety data. 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 within 3 days after IMP administration.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product

None

2.6.8.4. Laboratory findings

Across all trials, there were no trends in clinical laboratory evaluations associated with sebetralstat use. No patients in Phase 2-3 trials reported TEAEs associated with clinical laboratory evaluations that were considered related to the IMP.

One patient in KVD900-302 had a marked increase in ALT/AST levels of >5 x ULN. The increased ALT was reported as a non-serious TEAE and led to withdrawal of the IMP and discontinuation from the trial, occurred more than 3 days after IMP administration and was considered not related to the IMP by the investigator. This patient also experienced an SAE of viral meningitis, which preceded the ALT elevation and which was considered not related to the IMP.

Further evaluations were performed on patients in KVD900-302 who had elevations ≥1.5 x ULN in liver function tests. Shift tables for liver function tests did not reveal any clinically significant changes. Patients with AST/ALT >2 x ULN and bilirubin >1.5 x ULN were excluded from the Phase 3 trials; therefore, most patients had normal transaminase and bilirubin values at baseline. Further evaluation of LFTs revealed that transient transaminase elevations were infrequent overall and did not require further intervention. There were no cases that potentially met Hy's law criteria in the clinical development program.

In the Phase 1 non-DDI Safety Population, 1 subject (1.2%) who received sebetralstat >600 mg had a TEAE of haematology test abnormal considered by the investigator to be related to the IMP.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Intrinsic factors

Age Group

Overall, there were no notable differences in safety based on age group.

Paediatric population

Safety data are available for 21 paediatric patients (3.1% of the All-Subjects Safety Population). Overall in the Phase 2-3 Double-blind Safety Population (representing KVD900-301 trial data), TEAEs were reported for a single paediatric 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]. None of the events were considered related to the IMP, none were SAEs, and none led to trial discontinuation.

Geriatric population

Ten geriatric patients aged ≥65 years (1.5% of the All-Subjects Safety Population) participated in 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. In Phase 2-3 trials, 2 patients (2.3%) received 300 mg, 4 patients (2.6%) received 600 mg, and 4 patients (2.9%) received placebo. In Phase 1, all 4 geriatric subjects (3.1%) received sebetralstat 600 mg or equivalent. TEAEs were reported for a single geriatric patient in each of the sebetralstat treatment groups (1 patient [50.0%] who received 300 mg [1 moderate event of seasonal allergy] and 1 patient [25.0%] who received 600 mg [1 moderate event of COVID-19).None of the events reported were considered related to the IMP, none were SAEs, and none led to trial discontinuation. It is observed that black and elderly patients are underrepresented the applicant should comment and provide a substantiated discussion on whether differential efficacy or safety would be expected.

Race

KVD900-110 was a randomised, double-blind, placebo-controlled, single-administration trial to evaluate the safety, tolerability, PK, and pharmacodynamics of sebetralstat at 3 different dose levels (300 mg, 600 mg and 1200 mg) in healthy adult White, Chinese, and Japanese subjects. A total of 74 subjects enrolled in the trial. For each cohort between 6 and 7 subjects of each ethnicity were exposed. Two Japanese subjects experienced a total of 3 TEAEs (abdominal pain upper, headache, and epistaxis), all were considered mild in severity and 2 TEAEs (abdominal pain upper and headache) were considered related to sebetralstat. Two Chinese subjects experienced a total of 4 TEAEs (dizziness, diarrhoea, nausea, and abdominal pain upper) and all were considered mild in severity. All 4 TEAEs were considered related to sebetralstat. Two White subjects experienced a total of 2 TEAEs (both headache) and both were considered mild in severity. The 2 TEAEs were considered related to sebetralstat. One TEAE (dysmenorrhea) of moderate severity was reported in a subject who received placebo in this population. There were no clinically significant differences in safety between the populations.

Hepatic Impairment

An assessment of the impact of hepatic impairment on patients with HAE taking sebetralstat for the on-demand treatment of HAE attacks has been performed. Hepatic metabolism/excretion of sebetralstat in humans is >20% (data from KVD900-103), sebetralstat therefore met the criteria for further assessment in patients of varying hepatic function. KVD900-104 was an open-label trial that evaluated the PK, safety, and tolerability of a single administration of 600 mg sebetralstat in subjects with varying degrees of hepatic function. Twenty-four subjects formed 3 different groups based on hepatic function: 8 with mild hepatic impairment, 8 with moderate hepatic impairment and 8 with normal hepatic function. Subjects received a single administration of 600 mg sebetralstat and were subsequently monitored in-clinic for 72 hours. To the extent possible the 3 groups were balanced according to weight, age, and smoking status. Overall, 600 mg sebetralstat as a single oral administration 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.

In Phase 2-3 trials, patients were excluded from entering the trials if they had clinically significant hepatic impairment (defined as Child-Pugh B or C) or inadequate organ function based on ALT, AST, bilirubin direct, and international normalised ratio levels at Screening.

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 sebetralstat-related clinical renal safety findings in healthy subjects or patients with HAE, including reduced eGFR. A dedicated renal impairment trial was not required for sebetralstat program development.

Extrinsic Factors

Food Effect

When administered as a single administration of 600 mg under fed or fasted conditions in KVD900-101, there was no food effect on the safety and tolerability of sebetralstat tablets, with a similar safety profile.

Geographic Region

Phase 2-3 trials were conducted in 20 countries; the trials were conducted in geographic regions of Europe (62.9%), North America (22.5%), Japan (4.7%), and Rest of World (9.9%) (Australia and Israel in KVD900-301; Australia, Israel, and South Africa in KVD900-302). Phase 1 trials were conducted in the United States (81.6% of subjects) and United Kingdom (18.4% of subjects). Overall, there were no differences in incidence or type of TEAEs, and no differences in the pattern of TEAEs reported following sebetralstat or placebo, when analysed based on geographic region.

Use in Pregnancy and Lactation

No clinical data are available. No pregnancy was reported during any trial.

Overdose

No TEAEs of overdose have been reported. Dose levels up to 3,000 mg over a 2-hour period have been taken in the clinical development program (KVD900-109). No trends or changes to the safety profile were observed with this supratherapeutic dose level. No SAEs 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.

Drug Abuse

No drug dependency studies of sebetralstat have been conducted; however, on the basis of sebetralstat's pharmacology, there is no theoretical reason to expect any drug abuse potential.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

As sebetralstat does not act on the central nervous system and does not produce cardiodynamic effects, it will have no or negligible influence on the ability to drive or operate machinery. There were no AEs that reflected an impairment to mental ability across the entire development program.

Long-term use of Sebetralstat

In the long-term, open-label Phase 3 safety trial KVD900-302, as of the 31 Jan 2024 data cut-off date, the median number of months for patients to be enrolled is 3.21 (range: 0.3 to 13.5 months). 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. There were no trends in safety findings with treatment of multiple attacks and associated repeated exposure to sebetralstat over the duration of the trial. Sebetralstat was well tolerated

with a favourable safety profile. Additionally, in both the Phase 2 and 3 Treated Safety Population and the Phase 3 Second-administration Safety Population, there were no trends in TEAEs per patient-year based on number of treatment administrations or exposures.

Sebetralstat as short-term prophylaxis

Five patients in KVD900-302 received sebetralstat for a total of 8 short-term prophylactic treatments

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

For the assessment of safety data from patients exposed in DDI phase 1 studies, please see section 3.3.1.1 Pharmacokinetics.

2.6.8.9. Discontinuation due to adverse events

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 were considered by the investigator to be related to the IMP (events of skin burning sensation and nausea). 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.

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The evaluation of the safety of sebetralstat is based on 13 clinical studies, including 10 Phase 1 studies, 1 phase 2 study and 2 phase 3 studies. The phase 2 and 3 studies enrolled patients with type 1 or 2 HAE disease, representing the majority of patients in the clinical setting.

Development program

The phase I studies were both uncontrolled and placebo-controlled trials: bioavailability and tolerability studies, a study dedicated assessing the potential impact of mild and moderate hepatic impairment on the pharmacokinetics and tolerability of sebetralstat, a study assessing the safety in Asian subjects, a dedicated study on the potential impact of sebetralstat on the QT interval. The Scientific Advice issued by the EMA agreed that no study dedicated to renal impairment was mandatory considering the unregular frequency of administration (on-demand treatment of HAE attacks) and the dose administered in the phase 2 and 3 trials that led to the assumption that no accumulation of sebetralstat was to be particularly expected in patients.

Whilst data collected from the phase 2 and 3 studies KVD900-201 and KVD900-301 are considered pivotal due to the designs (double blind placebo controlled-studies), supportive data from the ongoing phase 3 open-label study KVD900-302 and from phase 1 studies contribute to the overall assessment of safety data. While in the phase 2 and 3 HAE attacks were each treated by 300mg (study KVD900-301) or 600mg (studies KVD900-201, KVD900-301, KVD900-302) when not treated by placebo, and by one additional dosing if considered necessary at least 3 hours after the first administration (except in study KVD900-201). The proposed dose recommendation in the SmPC for the treatment of an HAE attack is of 300 mg of sebetralstat followed by an additional 300 mg dose if still considered necessary. Considering this dose recommendation in the SmPC, it can be considered that the design of study 301 with its 600 mg arm and its cross over challenges the interpretation of the safety profile of the drug according to its future claimed posology. Indeed, the enrolled patients were expected to be treated for 3 attacks (on a duration of approximately 25 weeks). Each attack was treated by sebetralstat 300 mg, sebetralstat 600 mg or by placebo according to the order assigned by the randomisation, hence the assigned treatment changed for each attack and any observed TEAE was assigned to the last IMP dose that was administered before the TEAE occurrence. Without denying the benefit of a crossover design which can contribute to reduce the individual variability and which is an appropriate design for rare diseases, it adds a difficulty to assess safety data and especially the relatedness of an AE to the placebo or to the investigational product and to which dose, especially in case of frequent or close administrations. In addition, the objective of the study having been that each patient was treated for 3 attacks, meaning by only one exposure to 300 mg, is not considered sufficient controlled data to allow a proper safety assessment of tolerance for the claimed dose, nor for the 600 mg regimen. Random adverse events observed after treatment cannot be excluded since no trend analysis can be performed. In order to better characterise the safety profile of sebetralstat at the 300 mg dose, it would have been helpful if the protocol had included a longer duration of assessment with a higher objective for the minimum number of attacks in order to collect more randomised data on treatment with sebetralstat, especially on the 300 mg dose. The approach taken by the applicant for the design of the ongoing open-label safety study 302 to treat all patients with the 600 +/- 600 mg regimen for every HAE attack instead of the 300 mg regimen is also not completely understood as the major part of exposure to sebetralstat within the clinical development is eventually with the 600 mg regimen. This choice of dose recommendation has not been discussed by the applicant in the overview or summary of safety. This approach could be accepted from a safety point of view: for dose-dependent adverse reactions, the investigation of a higher dose could cover the major part of the safety profile but it should be taken into account that the assessment of the safety profile with 600 mg might not allow to completely and specifically characterise the safety profile of the 300 mg regimen as it could be possible that some ADRs are observed with low doses but unobserved with higher doses (for instance in case of an over-activated receptor or pharmacological target). It can therefore not be formally concluded that the characterisation of the safety profile of sebetralstat 600 mg will entirely include the dose-dependent ADRs of the 300 mg regimen. At last, for dose-independent ADRs, the amount of sebetralstat is of no relevance. Moreover, to a certain extent, it could be estimated that the safety results observed in patients treated on-demand by only one 600 mg dose could bring relevant supportive data to address the safety profile of the 2 tablets of 300 mg that are proposed to be recommended 3 hours apart for the treatment of an attack in the PI. The safety of the individual administration would not be addressed but the safety per day of treatment would be.

Study KVD900-302 also integrates the possibility for patients who need to undergo a medical procedure that could induce a HAE attack to take 3 doses of sebetralstat spaced at 6-hour intervals as a short-term prophylaxis, beginning 1 hour before the procedure.

The applicant presented aggregated safety data using 6 population pools including the phase 2 and 3 double-blind safety population for the randomised trials KVD900-201 and KVD900-301 and the phase 3 second administration safety pool for the assessment of repeated exposure, which is endorsed. For the phase 1 studies, the pools (non-DDI studies and DDI studies) are also acceptable since they include healthy subjects but it should be noted that the data come from studies that are not completely comparable from one another with different designs, very different amounts of sebetralstat doses and frequencies of administration.

Exposure

Safety of sebetralstat was evaluated in accordance with EMA SA as regards to the expected number of patients (approximately 200 HAE patients with 600 sebetralstat administrations for safety evaluation). A total of 670 subjects and patients treated by sebetralstat or by placebo have been included throughout all the phase 1, 2 and 3 studies, including 328 subjects in the non-DDI phase 1 studies and 213 patients in the phase 2 and 3 studies. Study 302 is still currently ongoing for 90 patients, while 74 patients completed the phase 2/3 studies without having rolled-over to the KVD900-302 study afterwards. 457 healthy subjects were enrolled in phase 1 studies and 452 completed the studies.

Among the 670 exposed people, 44 subjects received doses of less than 300 mg of sebetralstat in phase 1 non-DDI studies, 26 subjects and 86 patients received 300 mg in the phase 1 non-DDI and the phase 2-3 studies, 128 subjects and 151 patients received 600 mg in the phase 1 non-DDI and the phase 2-3 studies, 84 subjects received more than 600 mg in the phase 1 non-DDI studies, 74 subjects and 138 patients received the placebo in the phase 1 non-DDI and the phase 2-3 studies.

In the double blinded parts of phase 2 and 3 studies in total, 87 patients received 300 mg, 151 received 600 mg and 139 patients received the placebo. Of the 87 patients treated by 300 mg, 34 received 2 administrations per attack. The dose regimen that has been chosen to be recommended in the PI is therefore the one for which the least data have been collected. Slight discrepancies can appear in the presented data, as other figures show that among patients treated by 300 mg, 29 received the regimen 300 mg x 2 for the management of an HAE attack (and not 34), and 57 received one 300 mg dose, for a total of 115 administrations of 300 mg tablets in study KVD900-301 for 86 treated attacks. Patients treated with the 600 mg regimen during the phase 2 and 3 studies received 1103 administrations for 864 on-demand treatments. Exposure with the 300 mg regimen represents only around 10% of the total exposure to the 600 mg regimen throughout the clinical studies in patients. There were also in addition 8 short-term prophylaxis treatments in 5 patients using the 600 mg x 3 regimen (24 administrations) in study KVD900-302 but there were no prophylaxis using the 300 mg dose since this possibility of treatment was not introduced in the only trial investigating the 300 mg regimen (KVD900-301). The experience with the use of sebetralstat for short-term prophylaxis is therefore very limited but it is to note that the applicant did not seek an authorisation for this subtype of treatment. In phase 2 and 3 studies, 179 patients received at least 1 dose of sebetralstat, 166 patients received at least 2 doses, 43 patients received between 6 and 10 doses and 20 patients received more than 10 doses. The safety database is of limited size, but it is expected that safety profile can be sufficiently characterised.

In Phase 2-3 trials, mean (range) age was 37.0 years (13 to 77). 21 patients (9.9%) were adolescents ≥12 to <18 years old (only allowed in Phase 3). Five geriatrics patients have received sebetralstat. As low numbers of adolescents and elderly subjects is noted, it is not possible to conclude on safety profile in these groups. The majority of patients were White (86.4%); 7.0% of patients were Asian. Over half (58.7%) of patients were female. Most patients (83.6%) entered the trial using on-demand treatment only, while 16.4% of patients were taking stable long-term prophylactic treatment (only allowed in Phase 3).

In study KVD900-201, a randomised double blind crossover (placebo/600mg), 84 patients were enrolled, 68 were randomised (34 in each arm) but 53 patients completed the study as 15 patients were withdrawn due to a sufficient number of patients who had completed the study.

In KVD900-301 study, 136 patients were randomised and 110 received at least one attack treatment. 13 adolescents (13 to 17 years old) were enrolled. No short term prophylaxis with sebetralstat was authorised in the study. Among the 110 treated patients, 86 were treated for 2 attacks and 68 of them received a third treatment for a third attack. Each attack was treated by one of the IMPs (sebetralstat 300 mg, 600 mg or placebo). Study KVD900-301 was early terminated after each patient completed the pre-specified number of treated attacks, being after receiving a dose of each regimen (placebo, sebetralstat 300 mg and 600mg in the order assigned by the randomisation). Some of these patients (68) rolled-over to study 302. In total 42 patients discontinued the study and only 68 completed the study (received 3 attack treatments). In addition, the objective of the study being that each patient was treated for 3 attacks in pivotal study 301, meaning by only one exposure day to 300 mg, is not considered sufficient controlled data to allow a proper safety assessment of tolerance for the claimed dose, nor for the 600 mg dose. The protocol should have included a longer duration of assessment with a higher objective for the minimum number of attacks in order to collect more randomised data on treatment with sebetralstat, especially on the 300 mg dose since study KVD900-301 was the only placebo controlled and randomised trial to assess this regimen. However, while exposure to the 300 mg regimen is considered too limited due to the short observation time in study KVD900-301, more safety data are available for the 600 mg regimen which could be considered as valuable supportive data, particularly with the 600 mg x 1 tablet regimen (643 exposures as per the applicant's summary) which amounts to the same total daily dose than the 300 mg x 2 regimen recommended in the PI proposal.

Open-label long-term safety study 302 was still ongoing for 90 patients by the DLP of the initial submission (31 Jan 2024). Among the 118 screened patients, 113 had been enrolled up to the DLP and 84 of them had received at least one treatment dose of 600 mg. No more than 3 patients had been enrolled for more than a year at the date of the DLP, and only 22 had been enrolled for more than 6 months. This period of assessment for this study did not allow to gather enough long-term data nor repeated exposure data since only 33 patients had been treated for more than five attacks (the maximum amount of treated attacks for one patient was however 37). The number of attacks treated by 1 dose per 24h was 486, the number of attacks treated by 2 doses / 24h was 149 and the number of attacks treated by 3 or more doses of 5 (and were considered as a non-compliance to the protocol). Additional safety data had therefore been requested at first round of the procedure, and the applicant provided in response updated data by 14 September 2024. Fifty more patients (including 11 more adolescents) were enrolled and treated at least once by sebetralstat, making the total number of patients at 134 instead of 84. The median exposure duration within the study was 8.06 months (from 0.3 to 21.2 months), with 87 patients exposed for at least 6 months, 29 patients for at least 12 months and 5 patients exposed for at least 18 months by 14 September 2024. It can therefore be considered that reasonable long-term safety data are available. The median value of treated attacks was 8 (from 1 to 61 attacks), and 85 patients (63.4%) had more than 5 attacks. In total 1706 attacks were treated with sebetralstat 600 mg, of which 1298 were treated with one dose and 405 were treated with 2 doses. The extended data up to 14 September 2024 allows to retrieve more long-term exposure data with 29 patients who were exposed for at least one year.

Adverse events

Among the whole developmental program and by the DLP of 31 January 2024, 369 TEAEs were observed. In the phase 2 and 3 studies, 270 TEAEs were observed. In phase 2 and 3 blinded studies that allowed comparison (studies KVD900-201 and KVD900-301), numbers of TEAEs by treatment and by dose range

show that the tolerance in patients treated by sebetralstat was similar to the tolerance in the group treated by placebo. The proportion of patients with an AE was similar also, whether patients were treated by sebetralstat 300 mg (19.8 %, 20 TEAEs in 17 patients) or 600 mg (18.5 %, 39 TEAEs in 28 patients) or placebo (17.4 %, 34 TEAEs in 24 patients). In the phase 1 non-DDI studies, 99 TEAEs were observed. TEAEs were reported for 8 (18.2%) subjects who received less than 300 mg (8 TEAEs), 1 (3.8%) subject who received 300 mg (1 TEAE), 29 (22.7%) subjects who received 600 mg or equivalent (50 TEAEs), 15 (17.9%) subjects who received more than 600 mg (27 TEAEs), and 10 (13.5%) subjects who received placebo (13 TEAEs). It can therefore be noted that for each treatment group of patients treated by sebetralstat, the proportion of subjects with a TEAE is similar (around 20%), except for subjects treated by 300 mg in which 1 patient had a TEAE (3.8 %). No safety trend is seen through these data.

By 31 January 2024, upper respiratory tract infection and headache were the most reported TEAEs in the whole developmental program. Upper respiratory tract infection was observed in phase 2 and 3 studies in 2.3% of patients treated by 300 mg of sebetralstat, 1.3% of patients treated by 600 mg but especially in 4.3% of patients treated by placebo. In phase 1 non-DDI studies this TEAE was observed in 6.8% of patients treated by less than 300 mg of sebetralstat and by 0.8% of patients treated by 600 mg. In the phase 2 and 3 studies blinded safety set, headache was more frequently observed in patients treated by sebetralstat 600 mg (4.6%, 7 patients) than in patients treated by 300 mg (1.2%, 1 patient) or placebo (2.9%, 4 patients). Similarly in the phase I non-DDI studies headache was more frequently observed in patients treated by higher doses of sebetralstat (2.3% of subjects treated by less than 300 mg, 6.3% of subjects treated by 600 mg, 9.5% of subjects treated by more than 600 mg). In study 201, among the 68 patients, 25 experienced a total of 55 TEAEs after treatment by sebetralstat or placebo, among which 2 abdominal pain upper (in 2 patients), 3 nauseas (in 3 patients), 3 vomiting in 2 patients, 4 nasopharyngitis, 1 alanine aminotransferase increase, 1 blood pressure increase, 3 back pains (2 patients), 8 headaches (5 patients), 2 flushing (2 patients). In the randomised part of the study the proportion of patients experiencing a TEAE was higher after treatment by sebetralstat (24.1%) than after treatment with placebo (12.7%). In the pivotal placebo-controlled study KVD900-301, 20 TEAEs were reported for 17 (19.8%) patients in the 300 mg group, 18 TEAEs were reported for 14 (15.1%) patients in the 600 mg group and 24 TEAEs were reported for 17 (20.5%) patients in the placebo group. The most common TEAEs were headache and vomiting. 1 gingival bleeding, 1 alanine aminotransferase increase, 1 gamma-glutamyltransferase increased were also observed. The applicant identified fatigue and dyspepsia as adverse reactions to the 300mg regimen. In the long-term safety study KVD900-302, 153 TEAEs were observed in 47 patients. No particular trend of adverse events is seen from the list of observed PTs, however it is noted that 3 events of biliary cholic in 1 patient and 1 event of hepatosplenomegaly were observed, as well as 2 events of alanine aminotransferase increase in 2 patients, 2 aspartate aminotransferase increase in 2 patients and 1 gamma-glutamyltransferase increase. In the updated safety data from study KVD900-302, no safety concern was seen. 332 AEs were observed in 74 patients until 14 September 2024. 31 AEs in 12 patients were assessed as related to sebetralstat by the investigators and 6 led to treatment discontinuation in 5 patients. Sixteen SAEs were observed in 9 patients, but none was considered as related to sebetralstat. The rates of AEs between the 2 periods were comparable.

A total of 35 related TEAEs in phase 2 and 3 studies and 45 TEAEs in phase 1 studies were observed. In the double blinded safety population set, 2.3 % of the patients treated by sebetralstat 300 mg (2 patients), 4% (6 patients) of the patients treated by 600 mg and 4.3% (6 patients) of the patients treated by placebo had a related TEAE. The 2 related TEAES reported after sebetralstat 300 mg were dyspepsia and fatigue (both having not been related TEAEs for the placebo), the 7 related TEAEs reported after 600 mg were dyspepsia, abdominal pain upper, nausea, back pain, hot flush and 2 headaches (1 in 2 patients each) and the 7 related TEAEs reported after the placebo mg were anal incontinence, nausea, dysgeusia, menstruation irregular, rash

and 2 headaches (1 in 2 patients each). No firm conclusion can be drawn considering the results for patients treated by the placebo, but it is to note that patients treated by 600 mg observed twice as much related TEAEs than patients treated by 300 mg. In the phase I studies, related TEAEs were reported for 4 (9.1%) subjects who received less than 300 mg (4 ADRs), 1 (3.8%) subject who received 300 mg (1 ADR), 20 (15.6%) subjects who received 600 mg or equivalent (39 ADRs), 15 (17.9%) subjects who received more than 600 mg (25 ADRs), and 7 (9.5%) subjects who received placebo (10 ADRs). Headache was the only ADR reported for more than 5% of the subjects but considering the safety database for non-DDI studies (79 observed TEAEs), it is not considered completely appropriate to present safety results for TEAEs observed in more than 5% of the safety population only. In non-DDI phase I studies, the only patient who experienced a related TEAE after being exposed to sebetralstat 300 mg experienced an upper abdominal pain. The related TEAEs experienced after a 600 mg that occurred more than once (among 39 AEs in total) were constipation (4 occurrences), nausea (2), fatigue (3), dizziness (3), headache (8), lethargy (2). No cause of concern arises from these data, however given the quite low number of exposure days per patient, it would be unlikely for any trend to be observed. The following list of ADRs was included in section 4.8 of the SmPC back pain, dizziness, flushing, vomiting, nausea, abdominal pain, diarrhoea.

Six patients had a non-related serious adverse event after being exposed to sebetralstat (3 SAEs occurred for one of the patients) in studies KVD900-301 and KVD900-302 (no SAE was observed in the phase 1 or 2 studies). One SAE occurred in a patient treated by sebetralstat 300 mg, the other 7 SAEs occurred in patients treated by 600 mg but no particular trend was seen in the observed PTs. Two cases of diabetes mellitus (one in patient with plausible medical history) have been reported in phase 2 and 3 clinical trials, but both considered not related to sebetralstat. Two gastrointestinal bleeding have been reported in phase I studies (both assessed as related to sebetralstat by investigators): rectal haemorrhage and haematochezia. No additional cases have been reported in phase 3 studies.

There was no death. The applicant did not identify any AE of special interest throughout the studies. The applicant stated that the safety profile following laryngeal attacks was examined in an ad-hoc analysis and that no notable safety findings were found.

In phase 2 and 3 trials, cumulatively 49 patients discontinued trials due to Adverse Event (3 patients), Protocol Violation (1 patient), Lost to Follow-up (3 patients), Physician Decision (1 patient), Withdrawal by Participant (8 patients), Trial Termination by Sponsor (30 patients), Other (3 patients). Overall, across the developmental program among the patients or subjects treated by sebetralstat, 4 patients discontinued the trial KVD900-302 and 2 subjects discontinued the treatment in phase I studies KVD900-106 and KVD900-112 due to TEAEs. Of note, 2 of these TEAEs leading to study discontinuation / IMP withdrawal were increases of hepatic enzymes, one of them having been assessed as related to sebetralstat (AST increase in phase I study KVD900-106). In total 3 TEAEs leading to study discontinuation and IMP withdrawal were assessed as related to sebetralstat by the investigators, a skin burning sensation, a nausea and an AST increase. No major issue arises from these data.

Special populations and situations

The safety in special populations are presented by common intrinsic and extrinsic factors.

Age: Regarding age and paediatric patients, the applicant only provided safety data from the blinded controlled study KVD900-301 where one paediatric patient in each treatment group (sebetralstat 300 mg, 600 mg and placebo) reported a TEAE. No concern is observed from these data. The rate of the observed TEAs is of around 10% in the phase 2 and 3 studies for paediatric patients, which is lower than the rate observed in adults exposed in the phase 2 and 3 studies (between 17 and 20% depending on the treatment

category) which is explained by the low number of exposed paediatric patients, data should be thus interpreted with caution. 21 adolescents were included in the phase 2 and 3 trials which can comply with what was requested by the Paediatric Committee (at least 12 adolescents treated for at least 3 HAE attacks). Considering the claimed dose, the minimum exposition has not been reached since only 10 attacks were treated by sebetralstat 300 mg in an unknown number of patients (between 4 and 6) but from a safety point of view, it can be considered that the adolescents treated by the 600 mg regimen can bring supportive data.

Regarding the geriatric population (65 years old or more), 6 patients and 4 subjects were included in the sebetralstat studies. One patient received one exposure to 300 mg and 1 was exposed to twice a 300 mg dose (1 exposure day) in the phase 2 and 3 studies. No geriatric patient received a short-term prophylaxis. Among the phase 2 and 3 studies, 1 patient 65 or older had a non-serious, non-related TEAE after having been administered a 300 mg dose (2 geriatric patients had been exposed to a 300 mg dose), and among the 4 patients exposed to 600 mg, 1 reported a non-serious, non-related TEAE. No safety concerns are observed from these data (the TEAEs were seasonal allergy and COVID19 infection) but no conclusion can be drawn considering the few enrolled patients. Elderly patients were highly under-represented in sebetralstat trials. In addition to the global lack of information, the oldest included patient was 74 years old. No particular risk of product accumulation is expected considering the unique day of treatment, a special caution should however be made for patients older than 65 and treated regularly in case of frequent attacks, or with hepatic impairment. It is also wondered if this subgroup population could be the more at risk of bleeding due to their age and due also to more frequent use of antithrombotic drugs, considering the theoretical impact of sebetralstat on coagulation.

Race/ethnicity: In study KVD900-110 investigating sebetralstat in healthy White, Chinese, and Japanese subjects, no particular safety trend was detected regarding race but a global overview of safety data from all studies sorted by race or ethnicity among all trials is missing and should be provided. While 75 subjects (14.6%) in phase I studies were of black race / African American, only 1 patient (0.5%) of black race was enrolled in the phase 2/3 studies. It is observed that black patients were underrepresented in the phase 2 and 3 trials. This issue was discussed at the peer-review TC, and it was concluded that, according to the literature, there does not seem to be a biological plausibility for a difference in efficacy or safety profile.

Hepatic impairment: In study KVD900-104 in 24 subjects with mild or moderate hepatic impairment no TEAEs were observed, and abnormal laboratory results were found without clinical significance. No dose adaptation for patients with mild or moderate IH has been proposed in the PI.

Renal impairment: In the SA issued by the EMA, the CHMP had agreed that a dedicated renal impairment study was not mandatory since the pharmacokinetics of sebetralstat were not expected to be impacted by renal impairment and since no risk of product accumulation was foreseen by the applicant considering the dose regimen applied in clinical studies. The applicant stated that no safety finding was seen in the included patients with reduced glomerular filtration rate and provided a comparison of safety data between subjects and patients with reduced glomerular filtration rate at baseline (20.9% of the subjects and 10.3% of the patients) and subjects and patients without renal impairment.

No clinical data for use in pregnancy and lactation are available. No pregnancy was reported during the clinical development programme. No ADR in special population was identified based on the submitted data.

The tabulation of AE by special population had been requested to the applicant. The provided table showed no safety issue in special population by 14 September 2024.

No overdose situation per se occurred during the clinical program, higher doses than the ones proposed to be recommended in the PI were however administered in some of the studies, up to 3000 mg of sebetralstat

over a two-hour period in study KVD900-109. Of note, one subject exposed to a dose of 3000 mg in KVD900-109 study experienced 4 related non-serious TEAEs of headache, dizziness, nausea and vomiting.

Laboratory results

In the initial submission, the provided tables for laboratory results did not allow to properly assess the trends of results. But the applicant concluded that throughout the studies no clinically significant abnormal results were retrieved and that there were no changes related to food intake, to dose or to administrations amount, and that the values were similar whether the IMP was administered by tablets or capsules. The applicant provided as requested in response to LoQ the tables of categories of laboratory results, which do not show any particular impact of sebetralstat treatment when compared to baseline numbers. Values that were in the clinically significant high category were rarely reported. The dose range for which higher/lower values were seen when compared to baseline was the 600 mg dose, particularly for glomerular filtration rate, PT, INR. No safety concern is seen in these results except for the glomerular filtration rate which showed substantial shifts in phase I non-DDI studies at the 3 dose ranges of 300, 600 and >600 mg of sebetralstat. In the absence of clinical manifestation, this does not raise any concern.

Coagulation assessment was inconsistent throughout the clinical development. Values of aPTT and PT were recorded in most of phase 1 studies and in study KVD900-201 but not in studies KVD900-301 and KVD900-302 where only the INR was assessed, which is considered detrimental to the assessment especially for aPTT measurements that could have allowed to detect a decrease of FXIIa activity in the dedicated population with HAE. Indeed, the pharmacological action of suppression of plasma kallikrein includes suppression of generation of FXIIa, a theoretical concern therefore exists on a potential of sebetralstat to decrease the activation of the coagulation pathway and the formation of plasmin and therefore to induce a tendency in an increased risk of bleeding after treatment. Upon request, further discussion on the clinical manifestations of bleeding was provided and no data raised concerns. All cases of bleeding were confounded by other factors than IMP treatment. There were no clinically significant abnormal haemostasis results in phase I studies and some clinically significant abnormal results were found in phase II and III studies, but they were single events without temporal relationship with sebetralstat or were prolonged due to a medical condition or a concomitant medication. No impact was seen on coagulation in patients with abnormal liver enzymes values.

Regarding hepatotoxicity results, no problematically high value was recorded and some lower-than-normal hepatic enzymes values were also registered after treatment. In study 110 hepatic enzymes results have exceeded normal values in all treated groups (Japanese, Chinese and Caucasians) but they were not assessed as clinically significant. Of note, 2 TEAEs leading to study discontinuation / IMP withdrawal were increases of hepatic enzymes (including 1 sebetralstat related AST increase in phase I study KVD900-106). Considering the mainly hepatic route of elimination of sebetralstat and the observed abnormal laboratory results, a discussion on the potential impact of sebetralstat on human safety was requested. None of the relevant narratives on liver-related TEAE was compatible with sebetralstat being a cause of the TEAEs. Therefore, no major concern for hepatic toxicity has been observed.

Vital signs

In phase 2 and 3 studies no trend was seen in the recorded vital signs, in KVD900-302 study 2 non-related TEAEs of hypertension and heart rate increase were observed in 2 patients. The applicant provided tables of categorical results. No particular trend is however seen in these tables, except a slight trend of higher blood pressure results observed after sebetralstat treatment at the dose of 600 mg, including 4 high clinically significant values. Other high results can be seen in some instances but are also observed with the placebo or were already seen at baseline. It can be noted that post-baseline vital signs values were more likely to be out

of range in the phase I studies. No issue is seen in these results.

Cardiac monitoring

In the QT study KVD900-109, sebetralstat at the studied doses did not have a clinically relevant effect on heart rate or cardiac conduction, i.e., the PR and QRS intervals but LS mean ΔQTcF on sebetralstat was consistently higher than on placebo across post-dose time points, with the largest LS mean ΔΔQTcF across all post-dose time points at a significant 10.4 ms, observed at 5 hours post-dose. This makes the TQT study positive according to ICH E14. Analysis of moxifloxacin treated subjects confirmed assay sensitivity. In the concentration-QTc analysis, a linear model was fitted. The estimated slope of the sebetralstat concentrations in the concentration-QTc relationship was statistically significant: 0.00035 ms per ng/mL (90% CI: 0.000201 to 0.000496; P = 0.0003) with a statistically significant treatment effect-specific intercept of 1.84 ms. The effect on ΔΔQTcF can be predicted to 8.12 ms (90% CI: 5.69 to 10.55) at the geometric mean C_{max} of sebetralstat (18,023.1 ng/mL), which corresponds to molarities > 30µM, that may significantly block hERG *in vitro*. Therefore, the results from the cardiodynamic evaluation demonstrated that sebetralstat has a relevant effect on the QTc, with a ΔΔQTcF exceeding 10 ms at supra therapeutic doses.

During the review process it was agreed that the QT findings were mitigated (i.e. positive threshold of 10 ms but only at very high concentrations level well above therapeutic concentration) therefore an intermediate approach was recommended, i.e. not a contra-indication in relation to acquired or a congenital long QT syndrome and other restrictions but a warning given that there was no adequate ECG monitoring in clinical studies to derive full reassurance). Moreover, it was agreed that patients were considered at risk of QT prolongation only in the situation of cumulative risk factors (patients with a risk of enhanced sebetralstat concentration due to drug interaction or hepatic impairment, patients with an acquired or a congenital long QT syndrome, patients with electrolytical disorders, patients taking concomitantly taking a drug known to induce QT prolongation…). Sections 4.4 and 5.1 of the SmPC have been updated accordingly.

Physical examinations

The applicant did not provide any summary of the physical examinations findings and only concluded that no clear trend had been observed with the abnormal findings throughout the clinical development program. In the non-DDI phase I studies, no examination resulted in an abnormal observation. In the phase 2 and 3 studies some abnormal observations were made but no concern arises from these observations.

2.6.10. Conclusions on the clinical safety

Sebetralstat was well tolerated throughout the clinical developmental program. In double blind studies, TEAEs were reported in 20% of patients treated by sebetralstat 300 mg, 18.5% in patients treated with 600 mg and 17.4% of patients treated by the placebo. The most frequent TEAEs were headache (1.2%, 4.6%, 2.9% respectively for sebetralstat 300 mg, sebetralstat 600 mg, placebo), gastrointestinal disturbances, rash and AST/ALT increased. Cardiac monitoring in the QT dedicated study has allowed to detect a potential of sebetralstat to prolong the QT interval but only at supratherapeutic dose, which led to a warning in the SmPC. Overall, the safety profile of sebetralstat is considered well characterised.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned for sebetralstat. This is based on the absence of important identified risks, important potential risks, or missing information in the safety concerns for the product. The safety data obtained during clinical development indicate that routine pharmacovigilance activities are sufficient to ensure the ongoing monitoring of the product's safety profile.

2.7.3. Risk minimisation measures

No additional risk minimisation measures are required for sebetralstat. This is based on the absence of any safety concerns included in the list of safety concerns.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 03.07.2025. The EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ekterly (sebetralstat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HAE is caused by a C1-inhibitor deficiency (AOHC1-INH). It is a rare, chronic, debilitating, and potentially life-threatening disorder characterised by recurrent and often unpredictable attacks of BK-mediated swelling in many parts of the body, without the presence of hives.

HAE type 1 and type 2 account for approximately 90% and 10% of HAE cases with C1-INH deficiency, respectively. Both types of HAE are caused by a large variety of genetic mutations in the SERPING1 gene. These mutations result in production of reduced levels of functional C1-INH (HAE type 1) or normal levels of dysfunctional C1-INH (HAE type 2. In rare cases, patients have a third type of HAE, nC1-INH-HAE (international nomenclature: HAE-nC1INH) (formerly referred to as HAE type III), in which antigenic and functional C1-INH levels are normal.

If left untreated, attack symptoms will typically intensify over the first 12 to 36 hours, then gradually subside over 2 to 5 days. In patients with untreated or inadequately managed HAE attacks, the impact on quality of life is significant. Between attacks, patients may experience significant psychosocial burden due to the anxiety of when they may experience their next attack.

3.1.2. Available therapies and unmet medical need

Several therapeutic options are currently available for adult and paediatric patients in the applicant’s targeted indication.

Treatment of acute attacks of HEA (on demand treatments)					
Date in year	Commercial denomination	INN	Method of administration	Population	Mechanism of action
2008	FIRAZYR 30 mg solution for injection in pre-filled syringe	icatibant	SC	Adults, adolescents and children aged 2 years and older	Selective competitive antagonist at the bradykinin type 2 (B2) receptor)
2010	RUCONEST 2100 Units powder for solution for injection.	conestat alfa Recombinant human C1 inhibitor	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2011	CINRYZE 500 IU powder and solvent for solution for injection	Plasma Human C1-esterase inhibitor.	IV	Adults, adolescents and children aged 2 years and older	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2013	BERINERT 500 IU powder and solvent for solution for injection/infusion	Plasma Human C1-esterase inhibitor.	IV or slowly infusion	Adults and children	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin
2025	**EKTERLY 300 mg film-coated tablet**	**sebetralstat**	**Oral use**	**Adult and adolescents aged 12 years and older.**	**Inhibitor of plasma kallikrein**

Albeit being the second representative drug of the pharmacological class of chemical inhibitor of kallikrein, with berotralstat only approved for prophylactic use, sebetralstat would be the first representative of this class in the treatment of HAE attack. An orphan drug designation was granted by the EMA for sebetralstat for the treatment of hereditary angioedema translating the potentiality of the drug to address an unmet medical need in such a rare disease.

As illustrated in the table, sebetralstat would be also the first treatment of HAE attack to be given by oral route, which is expected to provide a particular convenience for patients. It is thus likely to induce a potential shift in the therapeutic management of attack of HAE in patients.

3.1.3. Main clinical studies

The clinical demonstration relies on a single randomised, placebo-controlled, pivotal study (KONFIDENT study or study KVD900-301) performed in adult and adolescent patients aged 12 years and older.

Patients were assigned to receive 3 treatments (300 mg, 600 mg or placebo) in randomised crossover fashion based on their assignment to 1 of 6 treatment sequences.

The trial population comprised 2 subsets (stratification criteria):

- patients who entered the trial taking only conventional on-demand treatment;
- patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment

The primary efficacy endpoint was the time to beginning of symptom relief, assessed using the Patient Reported Global Impression of Change (PGI-C). The PGI-C required patients to assess their attack symptoms using a seven-point scale ("much worse" to "much better"). To achieve the primary endpoint, a patient had to report a positive and sustained response on the PGI-C within 12 hours (2 time points).

A total of 110 patients treated at least 1 attack with IMP and were therefore included in FAS and the Safety Set. All 110 patients treated their first attack with IMP, 86 patients treated also their second attack with IMP, and 68 patients also treated their third attack with IMP, for a total of 264 treated attacks. Among the total of attacks treated in a cross over manner, there 87 treated with 300 mg of sebetralstat, 93 treated with 600 mg of sebetralstat, and 84 treated with placebo. Attacks ranged in severity from mild to very severe and occurred in all anatomic locations.

3.2. Favourable effects

The study design was cross over and primary endpoint was the time to the beginning of symptom relief.

There was a statistically significant (<0.0001) improvement in the time to the beginning of symptom relief between 300 mg KVD900 versus placebo group, with a clinically meaningful effect size of 1.61 hours (95% CI: 1.28, 2.27) for 300 mg KVD900 group versus 6.72 hours (95% CI: 2.33, not evaluable) for the placebo group. No apparent incremental benefit was observed with the 600 mg dose in the overall population.

Furthermore, there was a statistically significant improvement in the number of attacks that reached beginning of symptom relief within 12 hours of first IMP administration in the KVD900 treatment groups 300mg than placebo group: 66 [75.9%] attacks versus placebo group: 41 [48.8%] attacks). The benefit is reinforced by the consistency of the results on the key secondary endpoint notably Time to Reduction in Severity (Patient Global Impression of Severity) (adjusted p=0.0036) and Time to Complete Attack Resolution (adjusted p=0.0022).

86 patients (78.2%) were taking on-demand therapy only, and 24 patients (21.8%) were taking long-term prophylaxis (including berotralstat, lanadelumab, and C1-INH). The benefit was not only demonstrated in the subgroup of patients receiving on demand therapy only but was also statistically significant despite the small number of concerned patients and albeit an incremental benefit might have been challenging, in patients taking long-term prophylaxis.

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 (range: 6.0 to 130), 41 minutes for the 600 mg KVD900 group (range: 5.0 to 142), and 51 minutes for the placebo group (range: 6.0 to 166).

3.3. Uncertainties and limitations about favourable effects

Reliability of the clinical demonstration

The description of the pivotal phase 3 study is difficult to interpret due to several inconsistencies in the way the planned sample size and decision to stop the trial are reported in the protocol and in the study report.

Several terms (patients, completers and attacks) were unfortunately used interchangeably in the study protocol and statistical analysis plan. The uncertainty related to this lack of clarity will remain but is not thought, overall, to have had a meaningful impact on the study conclusions.

Limited number of paediatric patients (≥ 12 years)

Only 13 adolescent patients were included in the FAS, of which only 10 patients were treated for a seizure at the approved dose (300 mg). 23 adolescent patients were included in the open-label trial. While this population was limited, there is no a priori concern about a potential difference in efficacy and safety in adolescents compared to adults, and the medical need for convenient oral administration of HAE attacks is fully recognised.

Dose to be used for the more severe patients with laryngeal attack

Only 3% (n=8) of the attacks treated included laryngeal swelling, a potentially life-threatening situation in the clinical trials. In the phase 2 and 3 studies, severe laryngeal attacks were excluded. Through the clinical development, thirty-eight (14.4%) attacks were severe and 7 (2.7%) were very severe at the time of treatment. Results from the open-label trial included data on 32 additional attacks involving the larynx. Median (IQR) time to treatment was 11.5min (1.0-34.0); time to beginning of symptom relief, 1.72h (1.04-3.18); reduction in attack severity, 4.25h (1.22 >12) and complete attack resolution, 12.69h (5.11->24). These data were comparable to the results for the primary and key secondary endpoints for the HAE population studied in the KVD900-301 trial.

Other under-represented populations

Only 5 patients (3.6%) were >65 years. As elderly patients often experience different responses to treatments due to variations in metabolism, comorbidities and concomitant medications, this could potentially affect their symptom relief and overall treatment efficacy. Thus, the lack of data in elderly is adequately reported in the SmPC. It is noteworthy that very few black patients were enrolled in the pivotal study. This finding has been echoed in the literature. It is nevertheless acknowledged that there is no biological plausibility for a differential efficacy/safety.

3.4. Unfavourable effects

In the double blinded safety population set (phase 2 and 3), 2.3% of the patients treated by sebetralstat 300 mg (2 patients), 4% (6 patients) of the patients treated by 600 mg and 4.3% (6 patients) of the patients treated by placebo had a related TEAE. The 2 related TEAES reported after 300 mg were dyspepsia and fatigue (both having not been related TEAEs for the placebo).

Sebetralstat is characterised by a potential to prolongate the QT at supratherapeutic concentrations. Information on the potential for QT prolongation have been implemented after request in the sections 4.4 and 5.1 of the SmPC due to the risk associated to the concentration values that would be expected in situations with multiple risk factors. Also, it is considered that an enhanced cardiac monitoring and further characterisation in future clinical trials would be worth being implemented in order to have some reassurance on the risk of QT prolongation.

In the randomised part of phase II study KVD900-201, the proportion of patients experiencing a TEAE was higher after treatment by sebetralstat (24.1%) than after treatment with placebo (12.7%).

In the phase 2 and 3 studies, 270 TEAEs were observed by 31 Jan 2024. In phase 2 and 3 blinded controlled studies KVD900-201 and KVD900-301, the proportion of patients with an AE was indeed similar whether patients were treated by sebetralstat 300 mg (19.8 %, 20 TEAEs in 17 patients) or 600 mg (18.5 %, 39 TEAEs in 28 patients) or placebo (17.4 %, 34 TEAEs in 24 patients).

In the phase 2 and 3 studies blinded safety set, headache was more frequently observed in patients treated by sebetralstat 600 mg (4.6%, 7 patients) than in patients treated by 300 mg (1.2%, 1 patient) or placebo (2.9%, 4 patients). Similarly in the phase 1 non-DDI studies, headache was more frequently observed in patients treated by higher doses of sebetralstat (2.3% of subjects treated by less than 300 mg, 6.3% of subjects treated by 600 mg, 9.5% of subjects treated by more than 600 mg).

There was no trend seen in the severity of the TEAEs.

Among the patients or subjects treated by sebetralstat by 14 Sept 2024, 5 patients discontinued the trial KVD900-302 and 2 subjects discontinued the treatment in phase 1 studies KVD900-106 and KVD900-112 due to TEAEs. In total 3 TEAEs leading to study discontinuation and IMP withdrawal were assessed as related to sebetralstat by the investigators, a skin burning sensation, a nausea and an AST increase.

3.5. Uncertainties and limitations about unfavourable effects

Limitation of the safety database

It is observed that black patients were underrepresented in the phase 2 and 3 trials. This issue was discussed and it was concluded that, according to the literature, there does not seem to be a biological plausibility for a difference in efficacy or safety profile.

Limitations on the characterisation of the PK profile

It is noteworthy that the applicant did not specifically investigate a potential PK exposure - effect relationship for efficacy and safety endpoints which could have helped to better tailor dose recommendation for patients.

Use in patients with hepatic impairment

The cumulative effect of hepatic impairment and concomitant use with strong CYP3A4 inhibitors deserves further consideration. Indeed, C_{max} increase of 235% and an AUC increase of 520% for sebetralstat have been calculated in the presence of itraconazole which is a strong CYP3A4 inhibitor and no particular safety concern has been observed in the exposed subjects, however the study was conducted in less than 20 patients treated once, so uncertainties remain on the risks associated to drug-drug interactions with strong but also moderate CYP3A4 inhibitors. This issue is to be taken into account when considering the potential for QT prolongation at high supratherapeutic doses. This issue is also especially relevant in case of patients who would also present a hepatic impairment (at least moderate), warning on the need of a dose adjustment in the SmPC for patients having a moderate hepatic impairment and taking both a strong CYP3A4 inhibitor and has been included.

3.6. Effects Table

Table 9. Effects Table for Ekterly for Symptomatic Treatment of Acute Attacks of Hereditary Angioedema (HAE) in Adults and Adolescents aged 12 Years and Older

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint Time to the beginning of symptom relief	There was a statistically significant (<0.0001) improvement in the 300 mg KVD900 versus placebo group	hours	1.61 hours (95% CI: 1.28, 2.27) for 300 mg	6.72 hours (95% CI: 2.33, not evaluable)	See CI	KVD900-301
Key Secondary 1 / Time to reduction in severity	There was a statistically significant faster time to reduction in severity for 300 mg of sebetralstat (Bonferroni adjusted p = 0.0036) and 600 mg of sebetralstat (Bonferroni adjusted p = 0.0032) compared to placebo					KVD900-301
Key Secondary 2 / Time to complete attack resolution	There was a statistically significant faster time to complete attack resolution for 300 mg of sebetralstat (Bonferroni adjusted p = 0.0022) and 600 mg of sebetralstat (Bonferroni adjusted p < 0.0001) compared to placebo.					KVD900-301
Unfavourable Effects						
TEAEs	Proportion of patients with TEAEs: similar tolerance	%	19.8% with 300 mg and 18,5% with 600 mg	17.4% with placebo	Limited exposure, until 3 attacks treated per patient by each of the IMP at maximum	phase 2 and 3 blinded studies
Related TEAEs	Twice as much TEAEs than with placebo	%	24.1% with 600 mg	12.7%	Limited exposure, until 3 attacks treated per patient by each of the IMP at maximum	Randomised part of KVD900-201
SAEs	As much SAEs for each dose regimen	%	1.2% with 300 mg and 1,3% with 600mg	0%		Safety Set
QT prolongation	LS mean ΔΔQTcF on sebetralstat across all post-dose time points at a significant 10.4 ms				the upper margin of the ΔΔQTcF confidence interval exceeds 10 ms	Phase 1 dedicated QT study KVD900-109

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

As HAE is a rare disease, one pivotal study with a crossover design for marketing authorisation is considered acceptable given the strength of evidence observed in the present submission. The benefit is deemed as particularly clinically meaningful to complete attack resolution especially with oral route administration. The latter gives the medicine potential to offer major improvements for patients, shortening the time to

administration and reducing discomfort and possible side effects of parenterally administered conventional on-demand treatments. The benefit was not only demonstrated in the main subgroup of patients on demand therapy but was also statistically significant despite the small number of concerned patients and albeit an incremental benefit might have been challenging, in patients taking long-term prophylaxis.

Administration is critical for effective management of HAE attacks, especially the ones involving the larynx. The results presented demonstrate that sebetralstat, as an orally administered drug, can significantly shorten the time from onset of an HAE attack to medicine administration. This is deemed critical in reducing severity of the attack and consequently its duration. These results further confirm the benefit of sebetralstat as an orally administered on-demand treatment.

Sebetralstat safety database is of limited size. The most common TEAEs were gastrointestinal disturbances, headache, rash and AST/ALT increased. There exists a potential for QT prolongation and therefore a dedicated wording in the PI is included in section 4.4 of the SmPC. No clinical data for use in pregnancy and lactation are available.

3.7.2. Balance of benefits and risks

Sebetralstat represents a therapeutic advance for adolescent and adult patients due to its convenient oral administration with an adequate efficacy level and a safety profile that does not raise particular source of concern.

The clinical benefit of sebetralstat in the symptomatic treatment of acute attacks of HAE in adult and adolescent patients aged 12 years and older has been adequately demonstrated. The assessment of the safety profile, although based on limited data, is considered acceptable. Therefore, the CHMP considers than the benefit of sebetralstat outweighs its risks.

3.7.3. Additional considerations on the benefit-risk balance

The EMA received input from a patient organisation, Rare Diseases Europe (EURORDIS), regarding their experience, concerns and needs related to HAE and its treatment, as well as their expectations for an oral treatment.

Patient organisations estimate that 4 to 5% of patients do not respond well to existing treatments. The most commonly used treatments are administered parenterally (SC or IV) with most patients self-injecting at home, while some ask assistance from a family member or a healthcare provider. Low number of surveyed patients go to emergency services, noting that often healthcare professionals prefer to wait and see if the crisis gets worse before injecting the treatment, or might regress spontaneously, due to the high price.

Patients are aware that the earlier they treat, the better is. The time needed to go home or in a suitable place to self-inject can be significant (treatment is taken 4 hours after onset in average). An oral treatment could be taken immediately, further reducing the severity of the crisis, and probably its duration. With an oral product such as sebetralstat, and depending on its efficacy, patients taking prophylaxis could be interested to stop taking the prophylactic treatment and rely on sebetralstat in case of a crisis, that they can take immediately.

3.8. Conclusions

The overall benefit/risk balance of Ekterly in the symptomatic treatment of acute attacks of hereditary angioedema in adults and adolescents aged 12 years and older is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal product

The CHMP by consensus is of the opinion that Ekterly is not similar to Takhzyro within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ekterly is favourable in the following indication(s):

Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sebetralstat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0476/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.