EKTERLY® (SEBETRALSTAT) EU RISK MANAGEMENT PLAN

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[redacted]

List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
ALT	Alanine transaminase
aRMM	Additional Risk Minimisation Measure
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (code/classification)
AUC	Area under the concentration versus time curve
$AUC_{\%extrapolated}$	The percentage of the total area under the plasma concentration-time curve obtained by extrapolation
AUC_{0-24}	Area under the concentration versus time curve from the time of dosing to 24 hours
AUC_{0-inf} or AUC_{inf}	Area under the plasma concentration versus time curve extrapolated to infinity
AUC_{0-t}	Area under the plasma concentration versus time curve from the time of dosing to the last measurable concentration
B2	Bradykinin receptor B2
BCRP	Breast cancer resistance protein
BK	Bradykinin
BMI	Body Mass Index
%CV	Percentage of Coefficient of Variation
^{14}C	Carbon-14
C1-INH	C1-esterase inhibitor
C4	Complement factor 4
CI	Confidence Interval
CL/F	Apparent total body clearance
C_{max}	The maximum (or peak) plasma concentration
CNS	Central Nervous System
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLP	Data Lock Point
EC	Ethics Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EDC	Electronic data capture
EEA	European Economic Area

Abbreviation	Definition
EFD	Embryo-foetal development
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
F	Bioavailability
F1	First filial generation
F12	Factor XII
FAS	Full analysis set
FCT	Film-coated tablet
FDA	US Food and Drug Administration
FDP	Fixed-dose phase
FIH	First-in-human
FII, FIIa, FVIIa, FXa, FXIa, FXIIa, etc.	Factors II, IIa, VIIa, Xa, XIa, XIIa, etc.
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
H or h	Hour
HAE	Hereditary Angioedema
hERG	Human ether-a-go-go-related gene
HK	High molecular weight kininogen
HMW	High molecular weight
HR	Heart rate
HRT	Hormone replacement therapy
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IRB	Institutional Review Board
IV or iv	Intravenous
K_{el}	Elimination rate constant
KLK1	Tissue kallikrein-1
MATE2-K	Multidrug and toxin extrusion protein 2-K
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N or n	Number
NHP	Non-human primate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OAT1	Organic anion transporter 1
OATP	Organic anion transporting polypeptide
ODT	Oro-dispersible tablet
OECD	Organisation for Economic Co-operation and Development
PAES	Post-authorisation efficacy study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PIC	Powder in capsule
PK	Pharmacokinetics
PL	Package Leaflet
PPS	Per-protocol set
PSUR	Periodic Safety Update Report
PWG	Pathology Working Group
P-gp	P-glycoprotein
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Product Information
PK	Pharmacokinetic
PKa	Plasma Kallikrein
PT	Preferred Term (MedDRA)
PV	Pharmacovigilance
q2h	Every 2 hours
q4h	Every 4 hours
q8h	Every 8 hours
QD	Once daily (Latin, “quaque die”)
QPPV	Qualified Person responsible for Pharmacovigilance
QT	QT interval (ECG)
QTc	Corrected QT-interval
QTcF	Fridericia-corrected QT-interval

Abbreviation	Definition
RM	Risk Minimisation (or Risk Management)
RMP	Risk Management Plan
SAD	Single ascending dose
SD	Standard deviation
SERPING1	Serpin family G member 1 gene
SmPC	Summary of (medicinal) Product Characteristics
SOC	System Organ Class (MedDRA)
STP	Short-term prophylaxis
$T_{1/2}$ (or $t_{1/2}$)	Half-life
TEAE	Treatment-emergent adverse event
TID	Three times daily (Latin, “ter in die”)
T_{max}	Time to maximum (peak) drug concentration
TQT	Through QT (study)
VAS	Visual Analogue Scale
Vz/F	Apparent volume of distribution
µCi	Microcurie

Part I: Product(s) Overview

Table Part I-1: Product(s) Overview

Active Substance(s) (INN or common name)	Sebetralstat
Pharmacotherapeutic Group(s) (ATC Code)	B06AC08
Marketing Authorisation Applicant	KalVista Pharmaceuticals (Ireland) Ltd
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ekterly®
Marketing Authorisation Procedure	Centralised
Brief description of the product	Plasma kallikrein inhibitor
	Sebetralstat is a competitive, reversible inhibitor of plasma kallikrein (PKa). By inhibiting PKa, sebetralstat blocks the cleavage of high molecular weight kininogen (HK) and the subsequent generation of bradykinin (BK), thereby halting HAE attack progression which is associated with increased vascular permeability and oedema formation. Sebetralstat also suppresses the activation of positive feedback mechanism of the kallikrein-kinin system (KKS), thereby reducing factor XIIa (FXIIa) and additional PKa production.
Hyperlink to the Product Information	Refer to the proposed Product Information
Indication(s) in the EEA	*Proposed:* Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.
Dosage in the EEA	*Proposed:* The recommended dose is 300 mg Ekterly administered at the earliest recognition of an attack. A second dose may be taken 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. No more than two doses of 300 mg Ekterly should be administered in a 24 hour period.
Pharmaceutical Form(s) and Strengths	*Proposed:* Film-coated tablet. Each film-coated tablet contains 300 mg sebetralstat. Yellow, oval shaped (approximately 15.5 mm x 9 mm), biconvex tablets debossed with KalVista logo “K” on one side and “300” on the other side. oPA/Al/PVC with aluminium lidding blisters (1 film-coated tablet per blister). Pack size: 4 or 6 film-coated tablets. Not all pack sizes may be marketed.

Is/will the product be subject to additional monitoring in the EU	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Hereditary Angioedema

Hereditary Angioedema (HAE) 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 (Bernstein, 2018). It is an inherited autosomal dominant condition that results in either low levels of complement component 1 inhibitor (C1-INH) (HAE Type I) or normal levels of non-functioning C1-INH (HAE Type II) (Rosen, 1965; Germenis, 2016), which both allow spontaneous activation of the kallikrein-kinin system, leading to increased vascular permeability and subsequent oedema in mucosal or subcutaneous (SC) tissues.

The first onset of HAE symptoms is variable, occurring in most patients' first or second decade of life, with nearly half of patients experiencing symptoms by age 6 and approximately 90% of patients before age 20 (MacGinnitie, 2014; Frank, 2016). Characteristics of HAE attacks are heterogeneous among patients as well as across attacks within an individual patient (e.g. severity, location).

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 (Gower, 2011). On average, patients have HAE attacks every 1 to 3 weeks (Bernstein, 2018), consistent with the average frequency of attacks observed in the ongoing long-term open-label trial of sebetralstat (KVD900-302). However, attack frequency is unpredictable and can vary greatly among and within individual patients. The most common symptoms of HAE attacks include skin swelling, which may be disfiguring or functionally limiting, and abdominal pain and discomfort secondary to submucosal oedema; upper airway swelling involving the larynx or oropharynx may be life-threatening if left untreated. Multiple anatomic locations may be affected within the same attack, occurring simultaneously or consecutively. If left untreated, attack symptoms 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 considerable 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 (Bygum, 2017).

SI.2 Incidence and Prevalence

HAE is a rare disorder, comprising around 2% of clinical angioedema cases (Frank, 2023; Craig, 2009).

A comprehensive search using various search terms was conducted on PubMed and the internet, including Orpha.net, to determine the prevalence of HAE. Notably, epidemiological studies in the European Union (EU) focused on Type I and Type II HAE, excluding Type III HAE due to its recent definition. While surveys reported balanced gender distribution, acknowledging the rarity and poor awareness of HAE, some studies, such as the one in Spain by Roche et al., noted potential underestimation of prevalence (Roche, 2005).

Despite variations in study timelines, HAE prevalence in the EU consistently ranged between 1.09 and 1.55 per 100,000. Recognizing HAE as a rare disease with underdiagnosed cases, the estimated prevalence hovered between 1 in 10,000 and 1 in 100,000 in the general EU

population. Though this is below the EMA's 5 in 10,000 threshold for orphan designation, it contrasts with the agency's previous acceptance of a higher prevalence (0.5 in 10,000) for recent orphan designations for lanadelumab and berotralstat. Acknowledging potential delays in diagnosis, the Sponsor conservatively estimated the EU HAE prevalence at 0.5 in 10,000, suggesting approximately 26,000 patients in the EU based on the calculations mentioned above.

In conclusion, this conservative estimate incorporates diagnosed cases and underscores the challenges in accurately assessing HAE prevalence, emphasizing the need for more precise figures that account for undiagnosed patients.

SI.3 Demographics

Race

Hereditary angioedema affects people of all races and ethnicities, with no bias seen toward any ethnic group (Frank, 2023; Ghazi, 2013).

Sex

Hereditary angioedema occurs in men and women at equal rates, although women experience more severe attacks than men (MedlinePlus, 2023; Frank, 2023; Ghazi, 2013).

Type III HAE attacks often follow elevations in hormone levels in women during pregnancy or in those taking oestrogen-containing hormone replacement therapy (HRT), which may explain why type III attacks occur more frequently in women (Lumry, 2013).

Age

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).

Patients diagnosed at an earlier age tend to have more severe outcomes than patients whose symptoms begin later in life. Spontaneously acquired forms of HAE are typically present after the fourth decade of life. Only about 4% of patients will experience the first attack after age 40 (Bork, 2006).

Although mutations in the SERPING1 and F12 genes are present at birth in many patients with HAE, symptoms caused by C1-esterase inhibitor protein deficiency usually appear in the first or second decade of life. The severity of attacks increases around puberty, whereas swelling during childhood tends to be milder, less frequent, and less visible as abdominal symptoms are more common (Frank, 2023).

In one study, researchers analysed symptom presentation in 209 patients with HAE. In most patients, symptoms began during childhood or adolescence, with an average age of onset of 11.2±7.7 years (range, 1 - 40 years). Initial HAE attacks started in the first decade of life in 107 (51.2%) patients, in the second decade of life in 79 (37.8%) patients, and at later ages in 23 (11%) patients. In 15 (7.2%) patients, symptoms began within the first year of life (Bork, 2005).

Although HAE causes lifelong symptoms, some people with HAE report decreasing symptom severity with advancing age (Frank, 2023).

SI.4 Main Treatment Options

Treatment of HAE consists of prophylactic treatments to prevent attacks and acute treatments to treat attacks when they occur.

In HAE, the treatment of choice in acute attacks consists of replacement with a commercially available C1 inhibitor (C1-INH), a kallikrein inhibitor or a bradykinin receptor type 2 antagonist.

Current acute treatments for HAE attacks are listed in the following table.

Table SI-1: Current Acute Treatments for HAE

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

The current prophylactic treatments for HAE are listed in the following table.

Table SI-2: Current Prophylactic Treatments for HAE

Name	Type of Product	Route	Indication (HAE-specific)
Cinryze	Plasma-derived C1-INH	iv	Pre-procedure prevention of angioedema attacks in adults, adolescents, and children (2 years old and above) with HAE Routine prevention of angioedema attacks in adults, adolescents, and children (6 years old and above) with severe and recurrent HAE episodes, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment
Takhzyro (lanadelumab)	Plasma kallikrein inhibitor	sc	For routine prevention of recurrent attacks of HAE in patients aged 2 years and older
Orladeyo (berotralstat)	Plasma kallikrein inhibitor	oral	Routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older
Andembry (garadacimab)	Factor XII inhibitor	sc	Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

There is only one other oral therapy for HAE, Orladeyo (berotralstat). Orladeyo is approved for the routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older. While Orladeyo is an oral treatment, its indication (prevention of recurrent attacks) differs markedly from that for which sebetralstat has been developed – the treatment of acute HAE attacks.

In addition to the current treatment for HAE listed above, danazol and tranexamic acid have been used to prevent HAE.

SI.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

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

HAE attacks are episodic rather than continuous, and the frequency and severity of the attacks vary considerably among patients. On average, untreated patients can have an HAE attack every 1 to 3 weeks, with most episodes lasting around three days (Bygum, 2017; Bernstein, 2018). Oedema mainly affects subcutaneous tissue (face, upper or lower extremities, genitals), abdominal organs (stomach, intestines, bladder), and the upper airway (larynx, tongue), accounting for 46%, 33%, and 6% of reported attacks, respectively (Longhurst, 2012).

While upper airway attacks are less common, they are potentially life-threatening. A study shows that approximately 50% of all patients with HAE will experience a laryngeal attack during their lifetime (Bork, 2006). Laryngeal oedema may occur at any age and was shown to be the usual cause of HAE-related death in previous studies (Bork, 2012; Bork, 2003). In a pedigree analysis of 182 families (728 patients) with HAE investigating mortality due to laryngeal attacks, 70 patients died due to asphyxiation. Among those patients, 63 cases had not been previously diagnosed with HAE (Bork, 2012).

The mortality rate from undiagnosed HAE can be as high as 40%, primarily attributed to upper airway obstruction. Asphyxiation can occur in patients of any age in 20 minutes to 14 hours, and it has occurred in patients with no previous history of respiratory symptoms (Bork, 2003).

Episodes involving other areas of the body can be severely debilitating and affect a patient's quality of life. For instance, gastrointestinal oedema, which is much more common, can cause severe nausea, vomiting, and intense pain (Toscani, 2011).

In addition to the physical issues that HAE can cause, the variability and unpredictability of attacks have an immediate and long-term effect on a patient's quality of life. Patients have a significant psychosocial burden between attacks due to the anxiety of when they may experience their next episode. Many patients modify their lifestyles to accommodate their disease with restrictions in their careers, partnerships, and recreational activities (Bygum, 2017).

In a study of Greek patients using a disease-specific quality-of-life questionnaire, anxiety-related issues dominated. It was reported that 48% feared possible death from their next laryngeal attack, 47% had problems with their social life, and 44% of patients avoided trips away from home. Also, 20% of patients had lost or had to change their employment due to absences. Among children in the study, nearly 40% reported frequent absences from school (Psarros, 2014).

These results are typical of those seen in other studies. For example, in a Danish study, more than half of patients felt that HAE had a significant psychological impact on their lives and restricted their physical activities. Almost two-thirds of this cohort were concerned about the risk of suffocation (Bygum, 2017).

Part II: Module SII - Nonclinical Part of the Safety Specification

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicology: Sebetralstat was well tolerated in repeat dose studies in rats of up to 26 weeks duration. The principal findings in rat studies of all duration were histopathological changes in the liver, thyroid, adrenal, kidneys, and ovaries at doses ≥300 mg/kg/day.	In rats, the findings in liver, thyroid, adrenal, kidneys and ovaries were considered an adaptive response to sebetralstat administration. Due to the minimal nature of the findings, and an absence of cellular damage or functional impairment, these were considered non-adverse, therefore they are not relevant to administration of sebetralstat to humans. Exposure at the no observed adverse effect level (NOAEL) of 300 mg/kg/day in the 26-week rat study was 35x and 11x the anticipated exposure following a maximum recommended human dose (MRHD) of 900 mg, for AUC and C_{max} respectively.
The liver was the primary target organ in non-human primates (NHPs), identified following administration of high daily doses of sebetralstat in the 35-day repeat dose study. Twice weekly oral (gavage) administration of sebetralstat, up to and including 300 mg/kg/dose, was well tolerated in both the 13- and 26-week studies. In these two studies, findings in the liver of sebetralstat treated animals were comparable to those seen in control animals and no toxicological effects were observed; therefore, the NOAEL was 300 mg/kg/dose.	The twice weekly dosing regimen was used to reflect the intermittent pattern of administration in patients. In the 26-week intermittent dosing study there were no pathological or clinical chemistry changes indicative of an effect on the liver. The NOAEL in the 26-week study was 300 mg/kg/dose; exposure at this dose level is 1.5x and 1.1x the anticipated exposure following the MRHD of 900 mg, for AUC and C_{max} respectively.
There were no sebetralstat-related effects on fertility and early embryonic development (FEED) in the rat, on pre-natal and post-natal development (PPND) in the rat, and on embryo-fetal development (EFD) in rabbits (high dose NOAELs of 600, 450 and 300 mg/kg/day respectively).	Exposure at the NOAEL in the rat FEED study, rat PPND study, and rabbit EFD study were 46x, 18x and 13x of the AUC at the MRHD respectively.
In the embryo-foetal study in rats, embryo-foetal losses and a few major abnormalities (including cleft palate and interventricular septal defects), were observed in the high dose group (600 mg/kg/day). The NOAEL for both maternal and foetal toxicity was considered to be 300 mg/kg/day.	The NOAEL of 300 mg/kg/day provides exposure of 18x the AUC at the MRHD. Sebetralstat associated embryo-fetal harm was apparent at 600 mg/kg/day, at exposure 72x times of the AUC at the MRHD, therefore not considered clinically relevant. As a precautionary measure, it is recommended to avoid the use of sebetralstat during pregnancy.
Sebetralstat was negative in a comprehensive battery of genotoxicity assays demonstrating an absence of genotoxic potential.	No impact on human usage.
Sebetralstat was not carcinogenic in a 26-week study in transgenic mice. There were some small increases in benign tumours (liver, pituitary, testes, ovaries and uterus) in the 104-week rat carcinogenicity study.	Non-genotoxic modes of benign liver tumour induction in rats, in the absence of cytotoxicity, have been well characterized and are considered not relevant to humans. The neoplastic and non-neoplastic changes in the endocrine and reproductive systems were suggestive of a mild hormonal perturbation [with potential action on the

Key Safety findings (from non-clinical studies)	Relevance to human usage
	hypothalamic-pituitary-gonadal axis which slightly increased spontaneous tumour incidences. These types of changes in rats are commonly a consequence of altered endocrine hormone metabolism associated with xenobiotic-induced liver enlargement and enzyme induction and therefore are not considered to be relevant to humans The No Observed Effect Level (NOEL) for benign tumour formation was 30 mg/kg/day for males and 100 mg/kg/day for females. Exposure at the NOEL was 15x and 2.6x of the AUC at the MRHD for females and males respectively.
Safety pharmacology: In NHPs sebetralstat had no effect on cardiovascular function, including heart rate, BP and ECG parameters, QTc prolongation and other waveform morphologies. The NOAEL was determined to be 300 mg/kg, the highest dose tested. Sebetralstat had no effects on rat central and peripheral nervous system parameters in a battery of behavioural and physiological investigations (Irwin test) and there were no effects on respiratory parameters in rats, both studies dosed up to 1,000 mg/kg/day single dose.	A thorough QT clinical study was performed using doses of up to 3,000 mg (given as 900, 900 and 1,200 mg at 0, 1 and 2 hours) with no effect on cardiovascular function. Therefore, the NHP study has been superseded by clinical data at supra-therapeutic doses. No impact on human usage.
Other toxicity-related information or data: Sebetralstat does not have phototoxic potential.	No impact on human usage.

Part II: Module SIII - Clinical Trial Exposure

The development program for sebetralstat comprises ten Phase 1 trials in healthy adult volunteers (healthy subjects and subjects with hepatic impairment), one Phase 2 trial in adult patients with HAE, and two Phase 3 trials in adults and adolescent patients with HAE.

Table SIII-1: Description of Clinical Efficacy and Safety 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
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

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
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 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
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 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

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
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 of sebetralstat alone and in combination with itraconazole (**Part 1**), eltrombopag (**Part 2**), phenytoin (**Part 3**), or quinidine (**Part 4**)	**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 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	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 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	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
					administrations (1 × 300 mg tablet each) 1 hour prior to and 3 hours after a single administration of sebetralstat 600 mg on Day 1 of Period 2	
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 45.8 ± 8.21 years (28 - 54) Black or African American/white/other: 2/13/1	Healthy males and females between the ages of 18 and 55	Single administration of sebetralstat 600 mg (2 × 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
					Part 4: 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
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

Trial Number/ Status	Trial Design	Main Objectives	Total Enrolled Sex Mean Age±SD (Range) Race	Trial Population	Dosing Regimen	Safety Assessments
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 I or II						
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 I or II	**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, multicenter trial	Clinical efficacy, safety, and tolerabiilty 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 I or II	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 multicenter, 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 I or II 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

Below is a summary of the demographic characteristics of the sebetralstat safety population. The characteristics of the sebetralstat and placebo groups were similar in each research phase.

Table SIII-2: Demographic Profile of all Subjects Enrolled in Sebetralstat Clinical Trials (Safety Population)

	Phase 1 Trials (N=457)	Phase 2 and 3 Trials (N=213)	Overall (N=670)
Age (years)			
n	457	213	670
Mean (SD)	39.3 (10.97)	37.0 (14.59)	38.6 (12.27)
Median (Min, Max)	39.0 (19, 68)	36.0 (13, 77)	38.0 (13, 77)
Age Group, n (%)			
Paediatric (≥12 - <18 years)	0	21 (9.9%)	21 (3.1%)
Adults (≥18 to <65 years)	453 (99.1%)	186 (87.3%)	639 (95.4%)
Elderly (≥65 years)	4 (0.9%)	6 (2.8%)	10 (1.5%)
Sex, n (%)			
Female	119 (26.0%)	125 (58.7%)	244 (36.4%)
Male	338 (74.0%)	88 (41.3%)	426 (63.6%)
Race			
White	317 (69.4%)	184 (86.4%)	501 (74.8%)
Black or African American	75 (16.4%)	1 (0.5%)	76 (11.3%)
Asian	55 (12.0%)	15 (7.0%)	70 (10.4%)
American Indian or Alaska Native	3 (0.7%)	0	3 (0.4%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	0	2 (0.3%)
Multiple	5 (1.1%)	0	5 (0.7%)
Not Reported	0	6 (2.8%)	6 (0.9%)
Other	0	2 (0.9%)	2 (0.3%)
Missing	0	5 (2.3%)	5 (0.7%)

SIII.1 Exposure to Sebetralstat

The number of participants across the clinical development program is summarised by trial population and dose level in the table below. The clinical program included 670 unique trial participants who received at least one administration of IMP ([sebetralstat], placebo, or DDI co-medications). 213 participants were patients in Phase 2 and 3 trials, and 457 were healthy subjects in Phase 1 trials (129 in DDI trials and 328 in non-DDI trials).

Table SIII-3: Exposure to Sebetralstat in Clinical Studies

	Phase 1 Trials (N=457)	Phase 2 and 3 Trials (N=213)	Overall (N=670)
Number of participants (n, %) and number of exposures (m) to the following dose levels			
<300 mg sebetralstat	44 (9.6) 52	-	44 (6.6) 52
300 mg sebetralstat	26 (5.7) 26	57 (26.8) 57	83 (12.4) 83
300 mg x 2	-	29 (13.6) 29	29 (4.3) 29
600 mg (or equivalent[a]) sebetralstat	257 (56.2) 492	173 (81.2) 643	430 (64.2) 1,135
>600 mg sebetralstat	84 (18.4) 84	-	84 (12.5) 84
600 mg sebetralstat x 2	-	68 (31.9) 203	68 (10.1) 203
600 mg sebetralstat x 3		10 (4.7) 18	10 (1.5) 18
600 mg sebetralstat x 3 (short-term prophylaxis)	-	5 (2.3) 8	5 (0.7) 8
300 mg sebetralstat and above	367 (80.3) 602	208 (97.7) 958	575 (85.8) 1,560
600 mg sebetralstat and above	341 (74.6) 576	196 (92.0) 872	537 (80.1) 1,448
All Dose Levels	**411 (89.9) 654**	**208 (97.7) 958**	**619 (92.4) 1,612**
Number of administrations of ≥300 mg sebetralstat	367 (80.3) 734	208 (97.7) 1,236	575 (85.8) 1,970
Number of administrations of ≥300 mg sebetralstat – Paediatric	-	21 (9.9) 199	21 (3.1) 199
Number of administrations of ≥300 mg sebetralstat – Geriatric	4 (0.9) 4	5 (2.3) 37	9 (1.3) 41
Number of administrations of ≥600 mg sebetralstat	341 (74.6) 708	196 (92.0) 1,121	537 (80.1) 1,829

[a]Includes 500 mg ODT dose in KVD900-108, which was determined to be bioequivalent to a 600mg FCT dose. An administration was defined as each dose of IMP.
An exposure was defined as all IMP doses taken within a 24-hour period or taken to treat an individual acute HAE attack. Exposure and exposure period are used interchangeably.
Unless otherwise stated all results are inclusive of all ages and exposures. Paediatric defined as ages 12-17 years old (inclusive). Geriatric is defined as ages 65 years and older.

SIII.2 Phase 1 Clinical Trials

Table SIII-4: Phase 1 Clinical Trials

Study Identifier	Study Type
KVD900-101	A phase 1, randomised, double-blind, placebo-controlled, 3-part, single ascending dose study of the safety, tolerability, and pharmacokinetics of sebetralstat followed by crossover sub studies of sebetralstat formulations, and food effect in healthy male volunteers
KVD900-102	A phase 1, randomised, double-blind, placebo-controlled, multiple-administration, multiple-cohort study to evaluate the safety, tolerability, pharmacokinetics, and the change from baseline in QTc following administration of sebetralstat 100 mg FCTs in healthy adult subjects
KVD900-103	A phase I, open-label study of the absorption, metabolism, and excretion of [^{14}C]-sebetralstat following a single oral dose in healthy male subjects
KVD900-104	A phase I, open-label, pharmacokinetic and safety study of a single oral dose of 600 mg sebetralstat (2 x 300 mg FCTs) in subjects with mild, moderate, and normal hepatic function
KVD900-106	A phase 1, 4-part, 2-period, open-label, fixed-sequence study to evaluate the effects of multiple doses of itraconazole, eltrombopag, phenytoin and quinidine on the single-dose pharmacokinetics of sebetralstat in healthy adult subjects
KVD900-107	A phase 1, open-label, randomized, single-dose, 2-way cross-over bioequivalence study under fasted conditions comparing sebetralstat chewed (test) or intact (reference) FCTs (2 x 300 mg)
KVD900-108	A phase 1, open-label, randomized, single-dose, bioequivalence study of sebetralstat following administration of FCTs or ODT (orodispersible tablet) in healthy adult subjects
KVD900-109	A phase 1, 2-part sebetralstat Thorough QT (TQT) study
KVD900-110	A phase I, randomized, single-dose, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics following administration of sebetralstat film coated tablets in healthy adult Caucasian, Chinese, and Japanese volunteers
KVD900-112	A phase 1, 4-part, 2-period, open-label, fixed-sequence trial to evaluate the effects of verapamil, efavirenz, cimetidine, and modafinil on the single-dose pharmacokinetics of sebetralstat in healthy adult participants

KVD900-101 Summary

Study short name and title:

KVD900-101: A randomised, double-blind, placebo-controlled, single ascending dose study of the safety, tolerability, and pharmacokinetics of KVD900 [sebetralstat] followed by crossover sub-studies of KVD900 formulations, and food effect in healthy male volunteers

Rationale and study objectives:

KVD900-101 was a Phase I, first-in-human (FIH) study.

Primary Objectives:	To investigate the safety and tolerability of single doses of sebetralstat when dosed as powder in capsule (PIC) in healthy male volunteers (Part A). To investigate the safety and tolerability of a single dose of sebetralstat when dosed in tablet or capsule formulation in healthy male volunteers (Part B).
Secondary Objectives:	To investigate the pharmacokinetics (PK) of single doses of sebetralstat when dosed as PIC in healthy male volunteers (Part A). To investigate the PK of a single dose of sebetralstat when dosed in tablet or capsule formulation in healthy male volunteers (Part B). To investigate any food effect on the PK and tolerability of sebetralstat when dosed in tablet formulation to healthy male volunteers (Part C).
Exploratory Objectives:	To investigate the pharmacodynamics (PD) of single doses of sebetralstat when dosed as PIC in healthy male volunteers (Part A). To investigate the PD of a single dose of sebetralstat when dosed in tablet or capsule formulation in healthy male volunteers (Part B). To investigate any food effect on the PD of sebetralstat when dosed in tablet formulation in healthy male volunteers (Part C).

Study design:

The study comprised 3 parts. Part A was a randomised, double-blind, placebo-controlled, single-ascending dose (SAD) design to assess the safety, tolerability, PK and PD of sebetralstat PIC (sebetralstat capsule). Part B was a randomised, open-label, single-dose, crossover design to investigate the safety, tolerability, PK (relative bioavailability) and PD of two sebetralstat formulations (sebetralstat Capsule and sebetralstat 100 mg Uncoated Tablet). Part C was a randomised, open-label, single-dose, 2-way crossover, food effect design to investigate the effect of fed/fasted administration on the tolerability, PK and PD of sebetralstat 100 mg FCTs.

Study population:

Eighty-four (84) subjects were required to complete the study.

The study was conducted in healthy male subjects; therefore, participants were not expected to derive any therapeutic benefit from participating. A healthy subject population with carefully considered inclusion/exclusion criteria avoided the potential for interaction of sebetralstat with any underlying disease state or concomitant medication that patients may have needed to take while ensuring that subjects were fit and well enough for participation in the study.

Study results:

Sebetralstat was considered safe and well tolerated when administered as a single-dose of 5, 10, 20, 40, 80, 160, 300 and 600 mg capsules during Part A and as a single-dose of 100 mg sebetralstat capsule and tablet formulations during Part B.

When administered as single-doses of 5–600 mg sebetralstat capsules (Part A):

- 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 up to 4, 6, 8 and 10 h following 80, 160, 300 and 600 mg sebetralstat capsules, respectively (see PD report).
- C_{max} was proportional to dose across the dose range, but overall exposure (AUC) was greater than proportional to dose.
- The $t_{½}$ (geometric mean) ranged from 1.94–11.70 h across the dose range.

When administered as a single-dose of 100 mg sebetralstat tablet or capsule (Part B):

- Administration of the tablet resulted in an approximate 53% increase in C_{max} when compared to the capsule, although overall exposure (AUC) was considered bioequivalent between the formulations.
- T_{max} (median) was significantly shorter (faster) for tablet vs. capsule administration of sebetralstat. This, together with the increased C_{max} indicates a faster rate of absorption following tablet administration.

When administered as a single-dose of 600 mg sebetralstat tablet fed or fasted (Part C):

- There was no food effect on the safety and tolerability of sebetralstat tablets with a similar safety profile observed following fed and fasted administration.
- More than 50% inhibition of plasma kallikrein enzyme activity was observed between 10 min and 12 h and between 20 min and 12 h for fasted and fed groups, respectively (see PD report).
- Fed administration resulted in an approximate 29% decrease in C_{max} when compared to fasted administration, although no food effect was observed on overall exposure (AUC).
- T_{max} (median) was significantly longer (slower) for fed vs. fasted administration of sebetralstat. This, together with the reduced C_{max} indicates a slower rate of absorption following fed administration.

Milestones:

Final report: 14 June 2019

KVD900-102 Summary

Study short name and title:

KVD900-102: A Phase 1, Multiple-Dose, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and the Change from Baseline in QTc following Administration of KVD900 [sebetralstat] 100 mg Film-Coated Tablets in Healthy Adult Subjects

Rationale and study objectives:

Primary Objective:	To investigate the safety and tolerability of multiple doses of sebetralstat.
Secondary Objectives:	To investigate the PK of multiple doses of sebetralstat.
	To evaluate the effects of sebetralstat on ECG parameters, including concentration-QTc relationship, following administration of sebetralstat 100 mg FCTs to healthy adult subjects.
Exploratory Objectives:	To investigate the PD of multiple doses of sebetralstat.

Study design:

A phase 1, double-blind, placebo-controlled, multiple-dose, multiple-cohort study was conducted to evaluate the safety and tolerability of sebetralstat as well as the exposure-response relationship between plasma drug concentrations and the change from baseline in QTc (Cohorts 1-4) following administration of sebetralstat 100 mg FCTs to healthy adult subjects under fasted conditions.

Study population:

The study was conducted with 42 healthy, non-tobacco-, non-nicotine-using adult male and female subjects.

Study results:

Administration of sebetralstat appeared to be well tolerated. No SAEs were reported during the study, and no subjects were discontinued because of an AE. All reported AEs were considered “mild” in severity and had an outcome of “recovered/resolved” at the end of the study. Six AEs were considered to have a possible relationship to the study drug, three AEs were considered to have a probable relationship to the study drug, nine AEs were considered to have a remote relationship to the study drug, and one AE was considered unrelated to the study drug.

One subject in Cohort 2 exhibited a QTcF Interval increase from baseline >30 milliseconds one hour after initial dosing with sebetralstat. One subject exhibited a QTcF Interval increase from baseline >30 milliseconds eight hours after initial dosing with the placebo product. No subjects exhibited a QTcF Interval increase from baseline >60 milliseconds during the study.

Milestones:

Final report: 13 May 2020

KVD900-103 Summary

Study short name and title:

KVD900-103: A Phase I, Open-label Study of the Absorption, Metabolism, and Excretion of [^{14}C]-KVD900 Following a Single Oral Dose in Healthy Male Subjects

Rationale and study objectives:

This study aimed to determine the absorption, metabolism, and excretion of [^{14}C]-sebetralstat and to characterise and determine the metabolites present in plasma, urine, and faeces in healthy male subjects following a single oral administration. Knowledge of the metabolism and excretion of the parent drug and its metabolites is useful for evaluating the Metabolites in Safety Testing requirements elucidated in the FDA Guidance9 and ICH M3,10 and the likelihood of effects of renal or hepatic impairment on the disposition of sebetralstat and the likelihood for DDIs with sebetralstat.

Primary Objectives:

To determine the mass balance of total radioactivity from [^{14}C]-sebetralstat following a single oral dose of 600 mg.

To determine the routes and rates of elimination of total radioactivity from [^{14}C]-sebetralstat following a single oral dose of 600 mg.

To characterise the pharmacokinetics (PK) of sebetralstat and total radioactivity following a single oral administration of [^{14}C]-sebetralstat (600 mg) to healthy male subjects.

Secondary Objectives:

To determine the metabolite profiles in plasma, urine and faeces after a single oral dose of 600 mg [^{14}C]-sebetralstat.

To determine the chemical structure of metabolites in plasma, urine and faeces after a single oral dose of 600 mg [^{14}C]-sebetralstat.

To assess the safety and tolerability of [^{14}C]-sebetralstat when administered as a single oral dose of 600 mg to healthy male subjects.

Study design:

The study was a Phase I, open-label, non-randomised, single-dose study in healthy male subjects to investigate the absorption, metabolism and excretion of [^{14}C]-sebetralstat following a single oral dose.

Study population:

Six subjects were studied, and all received a single 600 mg dose of [^{14}C]-sebetralstat containing approximately 540 µCi of [^{14}C].

Study results:

Sebetralstat was rapidly absorbed in the systemic circulation, with a median t_{max} of 0.500 hours in plasma, and declined biphasically, with a geometric mean $t_{1/2}$ of 5.79 hours.

The overall mean recovery of radioactivity of a 600 mg dose of [^{14}C]-sebetralstat in urine and faeces was nearly complete over the observation period (95.8%). Faecal excretion was the predominant route of elimination for [^{14}C]-sebetralstat, with observed mean recovery of total radioactivity in urine and faeces of 32.4% and 63.4%, respectively.

After an oral dose, sebetralstat underwent extensive metabolism in human subjects. The main routes of biotransformation were via chain cleavage at two different points in the molecule (giving metabolites M19 and M10; M10 co-eluted in urine with a di-oxidation/di-hydrogenation product (M41)), a di-oxidation/di-hydrogenation product (M34) and the pyridyl desmethyl product M3.

Sebetralstat was the major circulating component in plasma. Metabolite M19, which is pharmacologically inactive, was the most abundant circulating metabolite in plasma, albeit <10% of the total radioactivity AUC_{0-24}. Sebetralstat was the most abundant component in both faeces and urine. The prevalence of metabolites in faeces and urine indicated that sebetralstat was eliminated in humans primarily via metabolism.

A single oral dose of 600 mg [^{14}C]-sebetralstat was well tolerated, with no treatment-related TEAEs reported when administered to healthy male subjects, and there were no safety findings observed in clinical laboratory evaluations, vital signs, ECGs or physical examinations.

Milestones:

Final report: 10 February 2021

KVD900-104 Summary

Study short name and title:

KVD900-104: A phase 1, open-label, staggered group, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of KVD900 [sebetralstat] in subjects with varying degrees of hepatic function.

Rationale and study objectives:

This clinical study pursued research to evaluate the impact of hepatic impairment on the PK of sebetralstat and followed the relevant FDA and EMA recommendations.

Primary Objectives:	To evaluate the impact of hepatic impairment on the plasma PK profile of a single oral dose of sebetralstat. To evaluate the safety and tolerability of a single oral dose of sebetralstat in subjects with hepatic impairment and with normal hepatic function.
Secondary Objective:	To evaluate the impact of hepatic impairment on secondary PK parameters of a single oral dose of sebetralstat.

Study design:

This was a phase 1, open-label, PK and safety study of a single oral dose of 600 mg sebetralstat in male and female subjects with mild hepatic impairment (Group 1, n=8), moderate hepatic impairment (Group 2, n=8), and normal hepatic function (Group 3, n=8). Assignment of the subjects to a hepatic impairment group was based on the Child-Pugh classification for assessing hepatic impairment at screening.

The study consisted of a 28-day screening period, an in-house assessment, and a follow-up visit. All subjects were confined to the study site from Day 1 (the day before dosing), administered a single oral dose of 600 mg sebetralstat on Day 1, and discharged from the study site on the morning of Day 4 after completing safety and PK assessments. The follow-up visit was scheduled for Day 14 (±2 days).

Study population:

Twenty-four (24) subjects were to be enrolled on this study: 16 subjects with hepatic impairment (8 subjects in each severity group) and 8 matching subjects with normal hepatic function. Subjects could be replaced, or additional subjects could be enrolled to ensure a minimum of 6 evaluable subjects per group.

Study results:

Following a single oral administration of 600 mg sebetralstat, the median times to peak concentrations were reached rapidly at 0.875 hours, 1.500 hours, and 1.125 hours post-dose in the normal hepatic function, mild, and moderate hepatic impairment groups. After reaching maximum levels, sebetralstat plasma concentrations declined gradually in all groups and were below the quantification limit in most subjects by the end of the sampling period at 72 hours. Profiles appeared similar across the normal hepatic function and mild hepatic impairment

groups. However, considerably higher plasma concentrations were observed for the moderate hepatic impairment subjects compared to the normal hepatic function group.

The geometric mean C_{max}, AUC_{0-t}, and AUC_{0-inf} of sebetralstat were comparable between mild hepatic impairment and normal hepatic function subjects. The geometric mean C_{max}, AUC_{0-t}, and AUC_{0-inf} of sebetralstat were approximately 1.6-fold, 2.0-fold, and 2.0-fold higher in moderate hepatic impairment than those with normal hepatic function. The geometric mean CL/F was comparable in mild hepatic impairment and lower in moderate hepatic impairment compared to normal hepatic function groups. The geometric mean Vz/F and $T_{1/2}$ were lower in mild and moderate hepatic impairment subjects than in normal hepatic function subjects.

These results indicate that sebetralstat systemic exposure was comparable in mild hepatic impairment and normal hepatic function groups. However, subjects with moderate hepatic impairment showed higher mean systemic exposures than subjects with normal hepatic function, indicating that moderate hepatic impairment impacted the PK of sebetralstat.

A summary of PK parameters is presented in the table below.

Table SIII-5: KVD900-104: Summary of The PK Parameters For Sebetralstat Following Single Oral Doses in Varying Hepatic Groups

Pharmacokinetic Parameter	Hepatic Impairment Group		
Number of Subjects	**Mild (N=8)**	**Moderate (N=8)**	**Normal (N=8)**
C_{max} (ng/mL) mean (min, max)	5,470 (2,670, 7,880)	8,510 (3,000, 13,800)	5,750 (2,140, 12,800)
T_{max} (h) median	1.500	1.125	0.875
AUC_{0-t} (h•ng/mL) mean (min, max)	21,900 (10,300, 38,700)	40,000 (20,400, 100,000)	20,300 (9,730, 45,400)
AUC_{inf} (h•ng/mL) mean (min, max)	21,900 (10,300, 38,800)	40,100 (20,500, 101,000)	20,400 (9,780, 45,600)
$T_{1/2}$ (h) mean (%CV) [n]	5.767 (52.2) [8]	6.851 (60.1) [7]	12.015 (33.7) [7]
CL/F (L/h) mean (%CV)	30.9 (40.0)	18.4 (38.3)	37.8 (45.6)
Vz/F (L) mean (%CV)	257 (60.5)	236 (96.3)	658 (48.6)

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Milestones:

Final report: 01 February 2023

KVD900-106 Summary

Study short name and title:

KVD900-106: A Phase 1, Four-Part, Open-Label, Fixed-Sequence Trial to Evaluate the Effects of Itraconazole, Eltrombopag, Phenytoin, and Quinidine on the Single-Dose Pharmacokinetics of KVD900 [sebetralstat] in Healthy Adult Participants

Rationale and study objectives:

Sebetralstat is predominantly metabolised by CYP3A4 and is a substrate of P-gp and BCRP transporters, thus rendering sebetralstat potentially susceptible to drug-drug-interactions when co-administered with CYP3A4 inhibitors/inducers and P-gp and BCRP inhibitors.

Part 1 of the trial assessed the effect of a strong CYP3A4 and P-gp inhibitor on the PK of sebetralstat. Itraconazole is a well-characterised, competitive, strong inhibitor of CYP3A4 and a potent P-gp inhibitor; thus, it was selected for this trial per the FDA Guidance for Drug Interaction Studies recommendations. All trial drugs were to be administered under fasting conditions in Part 1, as the bioavailability of the solution form of itraconazole is increased under fasting conditions (Sporanox®, 2024).

Part 2 of the trial assessed the effect of a potent BCRP inhibitor on the PK of sebetralstat. Eltrombopag is a well-characterised, competitive, potent inhibitor of BCRP and OATP, but not CYP3A4 nor P-gp; thus, it was selected for this trial as per recommendations in the FDA Guidance for Drug Interaction Studies. All trial drugs were to be administered under fasting conditions in Part 2, as the bioavailability of eltrombopag is increased under fasting conditions (Promacta®, 2023).

A fixed-sequence, crossover design, with the inhibitor administered in Period 2, was selected for each trial part. This reduced the trial duration and prevented any carryover effects of itraconazole or eltrombopag on CYP enzymes and P-gp or BCRP transporters by initiating each period with similar enzyme/transporter baseline activity levels. A crossover design reduces the residual variability as every participant acts as their own control.

The 4-day washout period between the sebetralstat dose in Period 1 and the first dose of itraconazole (Part 1) or eltrombopag (Part 2) in Period 2 is considered sufficient to prevent carryover effects of the treatments.

Women of non-childbearing potential were included in this trial based on information in itraconazole and eltrombopag monographs.

Part 3 and 4 only:

Phenytoin is a strong CYP3A4 inducer as designated by FDA and EMA. Induction of CYP3A4 can potentially reduce systemic exposure to sebetralstat and possibly reduce its efficacy. A strong CYP3A4 inducer is chosen to extrapolate the results to other CYP3A4 inducers. V.B.5. (FDA, 2020). Due to nitrosamine contamination during drug manufacturing, the most commonly utilised CYP3A4 inducer, rifampin, is no longer available in the US for use in DDI trials. Phenytoin is listed on the FDA website “Drug Development and Drug Interactions Table of Substrates, Inhibitors and Inducers” as a strong index CYP3A4 inducer.

Based on feedback from the FDA on the final protocol, it was noted that, in common with most strong index CYP3A4 inhibitors, itraconazole also inhibits P-gp. Sebetralstat is both metabolised predominantly through CYP3A4 and is a substrate of P-gp. Because itraconazole affects both pathways, if the DDI result from Part 1 did not fall within the no-effect boundaries, it may be challenging to determine which pathway affected sebetralstat PK. In that instance, as listed in FDA DDI guidance, it was recommended that further investigation be conducted to assess the impact of a P-gp inhibitor on the PK of sebetralstat. Although the FDA did not identify a P-gp-specific inhibitor (most will also inhibit some CYP isoform[s]), quinidine has been used in previous DDI trials in humans (Bui, 2016; Kotsuma, 2008).

The objective of Part 4 was to get a clearer understanding of what causes any DDI effect seen in Part 1. Therefore, quinidine was selected as a P-gp inhibitor. Quinidine is also a CYP2D6 inhibitor, but sebetralstat is not metabolised by this CYP isoform to any notable extent.

The trial dosing for quinidine divided 600 mg of quinidine into two doses of 300 mg each, administered 1 hour prior and 3 hours after dosing sebetralstat. The dosing at 3 hours ensured a sustained P-gp inhibition throughout the period of sebetralstat absorption since the sebetralstat mean plasma concentrations at 3 hours were approximately half of the mean C_{max}.

Sebetralstat, quinidine, and phenytoin were administered under fasting conditions as there were no safety concerns, and bioavailability was less variable.

A fixed-sequence, crossover design, with the inducer/inhibitor administered in Period 2, was selected for each trial part, which reduced the trial duration and prevented any carryover effects of phenytoin or quinidine on CYP enzymes and P-gp transporters by ensuring that each period was initiated with similar enzyme/transporter baseline activity levels.

A crossover design was used to reduce the residual variability, as every participant acted as their own control.

The 4-day washout period between the sebetralstat dose in Period 1 and the first dose of phenytoin (Part 3) or quinidine (Part 4) in Period 2 was considered sufficient to prevent carryover effects of the treatments.

Part 1 - Effect of itraconazole on sebetralstat

Primary Objective:	To determine the effect of multiple-dose itraconazole, a strong CYP3A4 and P-gp inhibitor, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of itraconazole in healthy adult participants.

Part 2 – Effect of eltrombopag on sebetralstat

Primary Objective:	To determine the effect of multiple-dose eltrombopag, a potent BCRP inhibitor, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of eltrombopag in healthy adult participants.

Part 3 – Effect of phenytoin on sebetralstat

Primary Objective:	To determine the effect of multiple-dose phenytoin, a strong CYP3A4 inducer, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of phenytoin in healthy adult participants.

Part 4 – Effect of quinidine on sebetralstat

Primary Objective:	To determine the effect of quinidine, a strong P-gp inhibitor, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with quinidine in healthy adult participants.

Study design:

The study was a Phase 1, four-part, open-label, fixed-sequence trial to evaluate the effects of itraconazole, eltrombopag, phenytoin, and quinidine on the single-dose pharmacokinetics of sebetralstat in healthy adult participants. Each of the four parts was to be conducted as an open-label, fixed-sequence, 2-period DDI trial. Trial parts could be conducted concurrently.

Study population:

Up to 64 participants were to be enrolled in the trial. Participants were to participate in only one part of the trial.

Parts 1 and 2:

A total of 32 healthy, adult, male and female (of non-childbearing potential) participants were to be enrolled, with 16 participants in Part 1 (itraconazole) and 16 participants in Part 2 (eltrombopag).

Parts 3 and 4:

A total of 32 adult male and female (of non-childbearing potential) participants were to be enrolled, with 16 participants in Part 3 (phenytoin) and 16 participants in Part 4 (quinidine).

Study results:

Pharmacokinetic results from this drug-drug interaction study demonstrated that sebetralstat is a sensitive substrate of CYP3A4. Metabolism of sebetralstat occurs mainly through CYP3A4-mediated metabolic pathways with minimal sensitivity to transporter inhibition. sebetralstat exhibited a >5-fold increase in AUC when administered with a strong CYP3A4 inhibitor and a >80% reduction in AUC when administered with a strong CYP3A4 inducer. Sebetralstat was not sensitive to P-gp or BCRP transporter inhibition.

In Part 1, the extent and peak of plasma sebetralstat exposures, as measured by $AUC_{0\text{-}inf}$ and C_{max}, were higher following itraconazole plus sebetralstat compared to sebetralstat alone. Following itraconazole plus sebetralstat, the median T_{max} was delayed compared to sebetralstat

alone, at 1.5 and 0.76 hours, respectively. The mean $T_{1/2}$ was slightly shorter, and mean CL/F and Vz/F values were lower following itraconazole plus sebetralstat than sebetralstat alone. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall exposures and peak exposure were 420% and 135% higher, respectively (GMR 90% CI for $AUC_{0\text{-inf}}$: 456%-594%; GMR 90% CI for C_{max}: 193%-287%), following itraconazole plus sebetralstat versus sebetralstat alone. Itraconazole is an inhibitor of CYP 3A4 and P-gp; to understand the potential contribution of P-gp to the effect seen in Part 1, Part 4 was conducted in this trial.

In Part 2, the extent and peak of plasma sebetralstat exposures, as measured by $AUC_{0\text{-inf}}$ and C_{max}, were similar following eltrombopag plus sebetralstat compared to sebetralstat alone. Following eltrombopag plus sebetralstat and sebetralstat alone, the median T_{max} and mean CL/F values were comparable. The mean $T_{1/2}$ was shorter, and the mean Vz/F was lower following eltrombopag plus sebetralstat relative to sebetralstat alone. The statistical comparisons of ln transformed plasma sebetralstat PK parameters demonstrated overall exposures were comparable, with the 90% CIs of the geometric mean ratios (GMRs) within the 80.00% to 125.00% reference interval. However, peak exposure was 12% higher (GMR 90% CI for C_{max}: 86%-145%) following eltrombopag plus sebetralstat versus sebetralstat alone. As eltrombopag increased sebetralstat peak exposure but not the extent of exposure, this suggests that eltrombopag weakly inhibited sebetralstat efflux transport mediated by BCRP.

In Part 3, the extent and peak of plasma sebetralstat exposures, as measured by $AUC_{0\text{-inf}}$ and C_{max}, were lower following phenytoin plus sebetralstat compared to sebetralstat alone. Following phenytoin plus v, the median T_{max} (0.65 hours) was slightly earlier relative to sebetralstat alone (0.75 hours), though a comparable range (minimum to maximum) was observed for the two treatments. The mean $T_{1/2}$ was similar, and mean CL/F and Vz/F values were higher following phenytoin plus sebetralstat than sebetralstat alone. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall exposures and peak exposure were 83% and 66% lower, respectively (GMR 90% CI for $AUC_{0\text{-inf}}$: 14%-21%; GMR 90% CI for C_{max}: 24%-46%), following phenytoin plus sebetralstat relative to sebetralstat alone. As phenytoin decreased sebetralstat exposure, this suggests that phenytoin-induced sebetralstat metabolism is mediated by CYP3A4.

In Part 4, the extent and peak of plasma sebetralstat exposures, as measured by $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max}, were higher following quinidine plus sebetralstat compared to sebetralstat alone. Following quinidine plus sebetralstat, the median T_{max} was slightly delayed relative to sebetralstat alone, at 1.0 and 0.85 hours, respectively. The mean $T_{1/2}$ was comparable following quinidine plus sebetralstat compared to sebetralstat alone, while mean CL/F and Vz/F values were similar for the two treatments. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall exposures and peak exposure were 14% and 18% higher, respectively (GMR 90% CI for $AUC_{0\text{-inf}}$: 97%-134%; GMR 90% CI for C_{max}: 88%-157%) following quinidine plus sebetralstat versus sebetralstat alone. As quinidine increased sebetralstat exposure, this suggests that quinidine inhibited sebetralstat transport mediated by P-gp. The small magnitude of this DDI indicates that inhibition of P-gp by itraconazole in Part 1 of the trial was a minor component and that the interaction seen in Part 1 was predominantly due to inhibition of CYP3A4 mediated metabolism.

A summary of PK parameters for each of the four study parts is presented in the table below.

Table SIII-6: KVD900-106: PK Parameters of Sebetralstat in the Presence of Itraconazole

Sebetralstat in the presence of a strong CYP3A4/P-gp inhibitor (itraconazole)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=17)**	**Sebetralstat+itraconazole (n=16)**	**Geometric Mean Ratio (%) [90%CI]**
C_{max} (ng/mL) mean (min, max)	5,470 (2,260, 15,700)	11,800 (8,580, 14,700)	235.4 [193.2-286.8]
T_{max} (h) median	0.76	1.5	-
$T_{1/2}$ (h) mean (%CV)	8.4 (31)	7.7 (18)	
Kel (h^{-1}) mean (%CV)	0.0920 (39.7)	0.0931 (16.5)	
CL/F (L/h) mean (%CV)	40.7 (31.0)	7.43 (26.0)	
Vz/F (L) mean (%CV)	503 (44.3)	80.7 (25.4)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	17,600 (10,800, 47,500)	86,100 (55,600, 145,000)	520.1 [455.8-593.5]

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Table SIII-7: KVD900-106: PK Parameters of Sebetralstat in the Presence of Phenytoin

Sebetralstat in the presence of a CYP3A4 inducer (phenytoin)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+phenytoin (n=16)**	**Geometric Mean Ratio [90%CI]**
C_{max} (ng/mL) mean (min, max)	5,620 (1,510, 16,200)	1,900 (689, 5,050)	033.6 [024.5-046.2]
T_{max} (h) median	0.75	0.65	-
$T_{1/2}$ (h) mean (%CV) [n]	8.8 (35) [16]	9.2 (65) [15]	
Kel (h^{-1}) mean (%CV) [n]	0.0871 (30.5) [16]	0.111 (69.5) [15]	
CL/F (L/h) mean (%CV) [n]	34.6 (28.1) [16]	206 (43.9) [15]	
Vz/F (L) mean (%CV) [n]	445 (45.9) [16]	2,990 (94.7) [15]	
$AUC_{0\text{-}inf}$ (h•ng/mL) [n] mean (min, max)	19,300 [16] (12,900, 41,100)	3,430 [15] (1,390, 6,930)	017.3 [014.4-020.7]

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Table SIII-8: KVD900-106: PK Parameters of Sebetralstat in the Presence of Eltrombopag

Sebetralstat in the presence of a BCRP inhibitor (eltrombopag)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+eltrombopag (n=16)**	**Geometric Mean Ratio [90%CI]**
C_{max} (ng/mL) mean (min, max)	4,540 (1,380, 11,000)	4,760 (1,950, 6,790)	111.6 [086.0-144.8]
T_{max} (h) median	1.1	1.1	-
$T_{1/2}$ (h) mean (%CV)	8.4 (38)	6.1 (36)	
Kel (h^{-1}) mean (%CV)	0.0948 (36.8)	0.130 (41.1)	
CL/F (L/h) mean (%CV)	40.3 (42.3)	38.3 (31.9)	
Vz/F (L) mean (%CV)	484 (53.0)	333 (47.7)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	17,000 (6,550, 27,500)	17,100 (8,870, 25,900)	102.6 [088.2-119.5]

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Table SIII-9: KVD900-106: PK Parameters in the Presence of Quinidine

Sebetralstat in the presence of a P-gp inhibitor (quinidine)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+quinidine (n=15)**	**Geometric Mean Ratio [90%CI]**
C_{max} (ng/mL) mean (min, max)	5,440 (2,290, 12,600)	6,570 (1,650, 11,900)	117.8 [088.2-157.1]
T_{max} (h) median	0.85	1.0	-
$T_{1/2}$ (h) mean (%CV)	8.3 (34)	7.1 (76)	
Kel (h^{-1}) mean (%CV)	0.0936 (37.0)	0.133 (43.6)	
CL/F (L/h) mean (%CV)	35.6 (37.3)	32.7 (51.5)	
Vz/F (L) mean (%CV)	464 (68.0)	430 (168)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	19,100 (8,710, 34,900)	22,400 (7,250, 43,700)	1.14.2 [097.1-134.3]

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Milestones:

Final report: 02 December 2022

KVD900-107 Summary

Study short name and title:

KVD900-107: An Open-Label, Randomised, Single-Dose, 2-Way Crossover Comparative Bioequivalence Study of KVD900 [sebetralstat] Following Administration of Chewed or Intact Tablets in Healthy Adult Subjects

Rationale and study objectives:

This bioequivalence study assessed the PK of chewed tablets versus intact tablets to ensure that drug exposure was comparable.

Healthy subjects were used for this study because it is more efficient to perform the study in healthy subjects, and it avoids the heterogeneity in patients that may make the comparison more difficult.

Subjects were to be randomised to treatment sequences to minimise assignment bias. A crossover design was used to reduce the residual variability, as every subject acted as their own control.

The 4-day washout period between the sebetralstat dose in Period 1 and Period 2 was considered sufficient to prevent carryover effects of the treatments.

Primary Objective:	To compare the single-dose PK of sebetralstat after administering chewed or intact tablets in healthy adult subjects.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat after administering chewed or intact tablets in healthy adult subjects.

Study design:

The study was an open-label, randomised, single-dose, 2-way crossover bioequivalence study under fasting conditions.

Screening of subjects was to occur within 28 days before the first dosing. On Day 1 of each period, a single dose of sebetralstat was administered as chewed (test) or intact (reference) tablets in a 2-period crossover fashion. Pharmacokinetic sampling for sebetralstat was conducted pre-dose and up to 48 hours after dosing.

There was a washout period of at least 4 days between doses.

Safety was monitored throughout the study by repeated clinical and laboratory evaluations. Discontinued subjects would not be replaced.

Study population:

Twenty-six (26) healthy adult male and female subjects were to be enrolled.

Study results:

A single oral dose of intact sebetralstat produced a mean plasma C_{max} of 6,733 ng/mL, whereas the mean C_{max} of the chewed tablets reached 8,117 ng/mL. Overall plasma sebetralstat exposure (based on $AUC_{0\text{-}inf)}$ was comparable with an 11% increase (90% CI for $AUC_{0\text{-}inf}$: 102.99%-120.31%). However, mean C_{max} was approximately 22% higher (90% CI: 108.19%-137.56%) following a single dose of 600 mg sebetralstat in chewed versus intact tablets. The median T_{max} was slightly earlier following chewed relative to intact tablets, at 0.792 and 1.251 hours, respectively, though a comparable range (minimum to maximum) was observed for the 2 treatments. Mean T1/2, CL/F, and Vz/F values were comparable between the 2 treatments.

This study was conducted as part of developing the sebetralstat ODT formulation and did not intend to administer a sebetralstat FCT by chewing or crushing. Sebetralstat FCTs should not be chewed or crushed and should be taken whole.

A summary of PK parameters is presented in the table below.

Table SIII-10: KVD900-107: PK Parameters of Intact versus Chewed Tablets

Pharmacokinetic Parameter	Intact Tablets	Chewed Tablets
Number of Subjects	**26**	**26**
C_{max} (ng/mL) mean (min, max)	6,733 (2,720, 11,500)	8,117 (3,450, 14,300)
T_{max} (h) median	1.251	0.792
$T_{1/2}$ (h) mean (%CV)	5.724 (39.7)	5.664 (44.5)
Kel (h^{-1}) mean (%CV)	0.1392 (37.3)	0.1456 (40.6)
CL/F (L/h) mean (%CV)	28.21 (40.4)	25.06 (36.8)
Vz/F (L) mean (%CV)	240.9 (67.1)	217.1 (69.6)
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	24,080 (10,900, 36,300)	26,620 (12,400, 45,400)

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Milestones:

Final report: 23 February 2022

KVD900-108 Summary

Study short name and title:

KVD900-108: An Open-Label, Randomised, Single-Dose, 3-Way Crossover Study to Assess the Comparative Bioavailability of KVD900 [sebetralstat] Following Administration of Orally Disintegrating Tablets (ODT) or Film-Coated Tablets in Healthy Adult Subjects

Rationale and study objectives:

In order to administer sebetralstat as an ODT to patients in a future Phase 3 study, PK data was needed after administering sebetralstat ODT. This comparative bioavailability study assessed the PK of ODTs versus FCTs swallowed whole under fasting conditions to determine if drug exposure was comparable.

In study KVD900-107, preliminary PK results showed that when chewed, the FCTs were not bioequivalent to the FCTs when ingested intact. The PK of the chewed tablet is anticipated to resemble that of the ODT. Dosed at 600 mg, the plasma exposure of sebetralstat, most notably C_{max}, was higher for the chewed tablets than the intact FCTs. Therefore, in addition to a 600 mg ODT dose, a lower dose of sebetralstat (i.e. 500 mg) was administered in this study as an ODT formulation.

Healthy subjects were used for this study because it is more efficient to perform the study in healthy subjects and avoids the heterogeneity in HAE patients, which may make the comparison more difficult.

Subjects were randomised to treatment sequences to minimise assignment bias. A crossover design was used to reduce the residual variability, as every subject acted as their own control.

Given the half-life of sebetralstat, the 4-day washout period between the sebetralstat dose in Period 1 and Period 2 and between the dose in Period 2 and 3 was considered sufficient to prevent carryover effects of the treatments.

Primary Objective:	To compare the single-dose PK of sebetralstat following administration of ODTs or FCTs in healthy adult subjects.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat following administration of ODTs or FCTs in healthy adult subjects under fasting conditions.

Study design:

An open-label, randomised, single-dose, 3-way crossover comparative bioavailability study.

Thirty-six (36) healthy, adult, male and female subjects were enrolled. Screening of subjects was to occur within 28 days before the first dosing.

On Day 1 of each period, a single dose of sebetralstat was administered at two different strengths as an ODT under fasting conditions (Treatment A or B) or as an FCT under fasting conditions (Treatment C) in a 3-period crossover fashion. Pharmacokinetic sampling for sebetralstat was conducted pre-dose and up to 48 hours after dosing.

There was a washout period of at least 4 days between the dose in Periods 1 and 2 and Periods 2 and 3.

Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects were not to be replaced.

Study population:

The trial population included healthy adult males or females of 18 to 55 years of age (inclusive) at Screening. Thirty-six subjects were enrolled.

Study results:

A single dose of 600 mg sebetralstat ODT produced a C_{max} of 6,770 ng/mL, whereas a single dose of 600 mg FCTs produced a C_{max} of 5,640 ng/mL. The median T_{max} and mean $t_{1/2}$, CL/F, and Vz/F values were comparable following 600 mg ODTs and 600 mg FCTs. Overall plasma sebetralstat exposure (based on $AUC_{0\text{-inf}}$) was slightly higher (90% CI for $AUC_{0\text{-inf}}$: 103%-119%), and peak exposure (based on C_{max}) was approximately 21% higher (90% CI: 108%-136%) following 600 mg sebetralstat ODTs versus 600 mg FCTs.

A single dose of 500 mg sebetralstat ODT produced a C_{max} of 5,520 ng/mL. Following 500 mg ODTs, the median T_{max} was slightly delayed relative to 600 mg FCTs at 1.3 and 0.99 hours, respectively. Mean $t_{1/2}$, CL/F, and Vz/F values were comparable among the treatments. Overall plasma sebetralstat exposure was slightly lower (90% CI for $AUC_{0\text{-inf}}$: 81%-94%), though peak exposure was comparable (90% CI: 90%-113%) following sebetralstat as 500 mg ODTs versus 600 mg FCTs.

A summary of PK parameters is presented in the table below.

Table SIII-11: KVD900-108: Pharmacokinetic Parameters FCTs vs ODT

Pharmacokinetic Parameter	600 mg Film-Coated Tablet	600 mg ODT	500 mg ODT
Number of Subjects	**36**	**36**	**36**
C_{max} (ng/mL) mean (min, max)	5,640 (1,440, 13,600)	6,770 (932, 12,100)	5,520 (1,190, 9,450)
T_{max} (h) median	0.99	0.99	1.3
$T_{1/2}$ (h) mean (%CV) [n]	8.9 (57) [35]	9.6 (67) [35]	9.4 (61) [36]
Kel (h^{-1}) mean (%CV) [n]	0.105 (55.4) [35]	0.0948 (49.3) [35]	0.104 (60.7) [36]
CL/F (L/h) mean (%CV) [n]	35.0 (39.2) [35]	30.7 (33.5) [35]	33.5 (41.9) [36]
Vz/F (L) mean (%CV) [n]	466 (84.3) [35]	426 (73.5) [35]	466 (86.3) [36]
$AUC_{0\text{-inf}}$ (h•ng/mL) [n] mean (min, max)	19,500 [35] (7,800, 31,800)	21,600 [35] (10,600, 37,200)	16,900 [36] (6,900, 28,200)

%CV: Percentage of Coefficient of Variation; Mean data are arithmetic means

Milestones: Final report: 24 August 2022

KVD900-109 Summary

Study short name and title:

KVD900-109: A thorough QT study evaluating the potential effect of KVD900 [sebetralstat] on electrocardiogram parameters in healthy subjects

Rationale and study objectives:

The purpose of this study was to investigate the effect of sebetralstat on cardiac repolarisation, as well as to provide a platform for the collection of any cardiovascular AEs. Previous clinical trials have not demonstrated any ECG-related AEs in study subjects; however, this study was intended to evaluate a supratherapeutic dose regimen not previously tested. The new higher dose allowed cardiac risk assessment at the highest expected clinical exposures. A single dose of moxifloxacin was used as a positive control to evaluate the study's sensitivity to detect increases in QT-interval measurements; the FDA has proposed using moxifloxacin in this manner. The study was necessary for the further development of sebetralstat and may benefit future subjects.

The trial was conducted per FDA and ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E14 (Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs - Scientific guideline) guidance.

Primary Objectives:	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: To evaluate the effect of a supratherapeutic dose regimen of sebetralstat on the Fridericia-corrected QT-interval (QTcF) in healthy subjects.
Secondary Objectives:	To evaluate the effect of a supratherapeutic dose of sebetralstat on other ECG parameters (heart rate [HR], PR and QRS intervals, treatment-emergent T-wave morphology, and U-wave appearance). To evaluate the PK of a supratherapeutic dose regimen of sebetralstat. To assess the safety and tolerability of a supratherapeutic dose regimen of sebetralstat. To evaluate the QTcF following the first and second dose of sebetralstat. To demonstrate the assay sensitivity of the study to detect a small QTc effect using a single dose of 400 mg oral moxifloxacin as a positive control.

Study design:

This study was a 2-part study.

Part 1 was an open-label single-treatment study to ensure that the proposed supratherapeutic dose regimen of sebetralstat to be used in Part 2 is safe and tolerable and that the targeted C_{max} levels are achieved; 2 sentinel dosing subjects administered active treatment were used in Part 1. Part 2 was a randomised, partially double-blind, placebo- and positive-controlled, 3-way crossover thorough QT (TQT) study to determine the cardiodynamic effects of sebetralstat relative to placebo.

After Part 1 was completed, the dose used in Part 2 was increased, and to mitigate the risk of this dose increase, a subset of 9 subjects in Part 2 was to be dosed first. During the washout period, after the first period was completed, a blinded safety data review was completed before the remaining subjects in Part 2 were dosed.

Study population:

A total of 38 healthy male and female subjects (8 subjects in Part 1 and 30 subjects in Part 2) were enrolled. Female subjects were of nonchildbearing potential or postmenopausal.

To ensure 24 evaluable subjects with data from all 3 treatment periods, 8 (Part 1) and 30 (Part 2) healthy male and female subjects were included in the study. Best efforts were made to recruit at least 30% of each gender in Part 2. No subject could participate in more than one study part.

In Part 1, 8 subjects were treated with a supratherapeutic dose of sebetralstat, 900 mg (3 x 300 mg sebetralstat), every 1 hour (q1h) for 3 doses (Hours 0, 1, and 2) to total 2,700 mg.

In Part 2, 30 subjects were randomised to ensure 24 evaluable subjects with data from all 3 treatment periods. On Day 1 of each period, subjects were given 1 of the 3 below study treatments; subjects were to receive all 3 study treatments by the end of Period 3:

- Treatment A: A supratherapeutic dose of 3,000 mg sebetralstat was given q1h for 3 doses as either 900 mg or 1,200 mg (3 x 300 mg or 4 x 300 mg sebetralstat, respectively); 900 mg (3 x 300 mg) was given at 0 and 1 hours and 1,200 mg (4 x 300 mg) was given at 2 hours.
- Treatment B: Placebo corresponding to the supratherapeutic sebetralstat treatment.
- Treatment C: Moxifloxacin 400 mg oral tablet, open-label, given at Hour 0 only.

Study results:

Safety

In Part 1 and Part 2, no deaths, SAEs, or other significant AEs were reported. One subject in Part 2 discontinued study treatment due to a TEAE of palpitations after treatment with moxifloxacin. The TEAE of palpitations was considered related to the study treatment (moxifloxacin) and mild in severity; the TEAE required no concomitant treatment and recovered/resolved by the end of the study. This subject did not receive subsequent doses of the study drug in Periods 2 and 3 of Part 2.

In Part 1, all 4 TEAEs reported were from 1 subject. Three of the 4 TEAEs were mild in severity, with 1 TEAE of headache that was considered moderate in severity. All 4 TEAEs were considered related to the study treatment of sebetralstat, and all TEAEs recovered/resolved by the end of the study. In Part 2, 14 TEAEs were reported by 8 subjects, all considered mild in severity. All TEAEs after sebetralstat treatment were considered related to the study treatment. The most commonly reported TEAEs were headache and nausea. All TEAEs in both Part 1 and Part 2 recovered/resolved by the end of the study.

Clinical laboratory tests showed an elevation of creatine phosphokinase in 1 subject, which was considered related to exercise and not related to any study drug. No other meaningful findings were reported with respect to clinical laboratory tests, and no clinically significant changes in vital signs or ECG measurements were reported.

Pharmacokinetics

Supratherapeutic doses of sebetralstat were administered to fasted healthy subjects every hour (q1h) at 900 mg for a total of 3 doses for Part 1 (total of 2,700 mg), and q1h at 900 mg for 2 doses, then at 1,200 mg for the third dose for Part 2 (total of 3,000 mg). Compared to the highest expected peak systemic exposure (C_{max}) of 29,370 ng/mL referenced in the protocol, the geometric mean C_{max} was 16.2% lower for Part 1 and 38.7% lower for Part 2. Overall systemic exposure was less than half of the highest expected overall systemic exposure (AUC) of 234,000 h•ng/mL. In addition, both geometric mean C_{max} and AUC did not increase with increasing the total dose from 2,700 mg in Part 1 to 3,000 mg in Part 2; however, individual exposures spanned similar ranges.

Absorption of sebetralstat was rapid, with concentrations peaking at a median of 3.00 hours for Part 1 and 2.75 hours for Part 2, relative to the first of the three sebetralstat doses (corresponding to 1.00 and 0.75 hours after the third dose). Concentrations declined monoexponentially, with geometric mean $T_{1/2}$ for Part 1 and for Part 2 being 2.25 and 3.24 hours, respectively.

Cardiodynamic Analysis

Sebetralstat at the studied dose did not have a clinically relevant effect on heart rate or cardiac conduction, i.e., the PR and QRS intervals. Although LS mean ΔQTcF on sebetralstat was consistently somewhat higher than on placebo across post-dose time points, and the largest LS mean ΔΔQTcF on sebetralstat across all post-dose time points was 10.4 ms, observed at 5 hours post-dose.

In the concentration-QTc analysis, a linear model with a treatment effect-specific intercept was fitted for sebetralstat plasma concentrations, which represented the data in an acceptable way. The estimated slope of the sebetralstat concentrations in the concentration-QTc relationship was shallow and 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).

Analysis of moxifloxacin-treated subjects confirmed assay sensitivity, and therefore, the results from the cardiodynamic evaluation demonstrated that sebetralstat has no clinically relevant effect on heart rate or cardiac conduction (i.e., the PR and QRS intervals). Based on this concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to sebetralstat plasma concentrations of ~16,900 ng/mL.

<u>Conclusions</u>

Safety

- Overall, 2,700 mg (3 doses of 3 x 300 mg) and 3,000 mg (2 doses of 3 x 300 mg and 1 dose of 4 x 300 mg) of sebetralstat were well tolerated in healthy subjects.

Pharmacokinetics

- Changes in sebetralstat exposure at 2,700 mg and 3,000 mg appear to be nonlinear as both C_{max} and AUC did not increase with increasing dose, and individual exposures spanned similar ranges.

Cardiodynamic Analysis

- Assay sensitivity was confirmed with moxifloxacin treatment.
- Sebetralstat has no clinically relevant effect on heart rate or cardiac conduction.
- An effect on ΔΔQTcF exceeding 10 ms can be excluded up to plasma concentrations of ~16,900 ng/mL.

Milestones:

Final report: 31 January 2024

KVD900-110 Summary

Study short name and title:

KVD900-110: A Single-Dose, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics following Administration of KVD900 [sebetralstat] Film Coated Tablets in Healthy Adult Caucasian, Chinese, and Japanese Volunteers

Rationale and study objectives:

This Phase 1 trial was planned to assess the safety, tolerability, and pharmacokinetics (PK) of a single dose of sebetralstat and its pharmacodynamic (PD) effects in healthy Japanese, Chinese, and Caucasian subjects.

Primary Objective:	To assess the safety, tolerability, and PK of a single dose of sebetralstat in Japanese, Chinese, and Caucasian subjects.
Secondary Objective:	To assess the PKa enzyme activity as a PD biomarker.
Exploratory Objective:	To assess the cardiac repolarisation (QTc) effects in the Japanese and Chinese populations and to compare it with Caucasian trial subjects.

Study design:

The study was a randomised, double-blind, placebo-controlled, single-dose ethno-bridging trial of orally administered sebetralstat in healthy Japanese, Chinese, and Caucasian adult male and female subjects. The trial was designed to assess the safety, tolerability, PK, and PD of sebetralstat. The Caucasian subjects were intended to serve as a control.

Study population:

A total of 72 healthy male and female subjects, 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18.5 and 32.0 kg/m^2 (24 Japanese, 24 Chinese, and 24 Caucasian subjects), were planned for enrolment.

The trial consisted of three dose levels with eight subjects per dose level/ethnic population. Of the eight subjects in each ethnic population, six were to be randomised to receive sebetralstat, and two were to be randomised to receive matching, blinded placebo.

Study results:

Following single doses of 300 mg, 600 mg, and 1,200 mg sebetralstat, plasma concentrations exhibited high variability for most time points. Following single doses of 300 mg to 1,200 mg, the median T_{max} ranged from 0.64 hours to 1.29 hours post-dose, which did not appear to be dose-dependent and was comparable across all ethnic populations. Following single doses of 300 mg to 1,200 mg, the arithmetic mean T1/2 of sebetralstat was 3.492 hours–6.912 hours, comparable across ethnic populations.

The mean C_{max} following a single dose of sebetralstat 300 mg was 3,511 ng/mL and 3,173 ng/mL in Japanese and Chinese participants, respectively. This was higher compared to Caucasian participants (2,490 ng/mL); however, there was substantial overlap between the groups. The C_{max} following a single dose of 600 mg was comparable between the ethnic groups (means 6,375 ng/mL–6,777 ng/mL). Following a single 1,200 mg dose, the mean C_{max} was

10,390 ng/mL and 9,292 ng/mL in Japanese and Chinese participants, respectively, and this was higher compared to Caucasian participants (5,997 ng/mL). However, there was substantial overlap between the groups.

Sebetralstat mean of $AUC_{0\text{-}inf}$ ranged from 7,882 h•ng/mL-8,352 h•ng/mL, and 17,050 h•ng/mL–18,980 h•ng/mL following single doses of 300 mg and 600 mg, respectively, and there was no apparent difference between the ethnic populations. Following a 1,200 mg dose of sebetralstat, the mean $AUC_{0\text{-}inf}$ was 33,410 h•ng/mL in Chinese participants and was considered higher compared to Japanese (23,020 h•ng/mL) and Caucasian (25,740 h•ng/mL) participants. However, there was substantial overlap between the groups.

A summary of PK parameters is presented in the table below.

Table SIII-12: KVD900-110: PK Parameters by Dose and Ethnicity

Pharmacokinetic Parameter	White	Japanese	Chinese	Pooled
Number of Subjects	**N=18**	**N=18**	**N=18**	**N=18**
300 mg	**n=6**	**n=6**	**n=6**	**n=18**
$AUC_{0\text{-}inf}$ (h•ng/mL)	8,190 (22.2)	7,500 (50.4)	7,730 (22.7)	7,798 (31.9)
$AUC_{0\text{-}t}$ (h•ng/mL)	8,160 (22.3)	7,460 (51.2)	7,710 (22.7)	7,772 (32.2)
C_{max} (ng/mL)	2,240 (53.7)	2,830 (90.4)	3,170 (20.6)	2,722 (57.4)
T_{max} (h)	1.29 (0.95, 1.60)	1.26 (0.55, 1.75)	1.00 (0.62, 1.25)	1.04 (0.55, 1.75)
K_{el} (1/h)	0.165 ± 0.0420	0.207 ± 0.0566	0.200 ± 0.0220	0.191 ± 0.0444
$t_{1/2}$ (h)	4.42 ± 0.965	3.75 ± 1.75	3.49 ± 0.371	3.89 ± 1.18
CL/F (L/h)	37.4 ± 8.46	43.9 ± 20.7	39.7 ± 9.29	40.3 ± 13.4
Vz/F (L)	233 ± 48.3	274 ± 285	200 ± 52.4	236 ± 162
600 mg	**n=6**	**n=6**	**n=6**	**n=18**
$AUC_{0\text{-}inf}$ (h•ng/mL)	16,400 (31.8) [n=5]	16,600 (64.8)	16,100 (42.9) [n=5]	16,390 (45.4) [n=16]
$AUC_{0\text{-}t}$ (h•ng/mL)	16,200 (28.2)	16,400 (66.8)	15,600 (39.3)	16,060 (43.6)
C_{max} (ng/mL)	5,960 (41.4)	6,180 (51.8)	5,200 (92.0)	5,763 (59.4)
T_{max} (h)	1.00 (0.50, 1.25)	0.99 (0.50, 1.50)	0.64 (0.27, 1.48)	0.99 (0.27, 1.50)
K_{el} (1/h)	0.128 ± 0.0271	0.136 ± 0.0517 [n=5]	0.182 ± 0.0508 [n=5]	0.148 ± 0.0483 [n=16]
$t_{1/2}$ (h)	5.65 ± 1.49 [n=5]	6.07 ± 3.32	4.03 ± 0.968 [n=5]	5.30 ± 2.31 [n=16]
CL/F (L/h)	36.6 ± 11.4 [n=5]	41.9 ± 25.2	40.2 ± 20.0 [n=5]	40.1 ± 18.9 [n=16]
Vz/F (L)	304 ± 96.3 [n=5]	438 ± 493	247 ± 180 [n=5]	337 ± 315 [n=16]

Pharmacokinetic Parameter	White	Japanese	Chinese	Pooled
1,200 mg	**n=6**	**n=6**	**n=6**	**n=18**
$AUC_{0\text{-}inf}$ (h•ng/mL)	24,500 (35.5)	21,800 (39.0) [n=4]	30,500 (49.2)	25,820 (41.7) [n=16]
$AUC_{0\text{-}t}$ (h•ng/mL)	23,700 (35.2)	23,500 (62.8)	30,100 (50.1)	25,580 (48.6)
C_{max} (ng/mL)	5,750 (31.6)	7,740 (112)	7,650 (78.8)	6,978 (73.2)
T_{max} (h)	1.02 (1.00, 1.50)	0.75 (0.50, 4.00)	1.16 (0.73, 3.00)	1.00 (0.50, 4.00)
K_{el} (1/h)	0.121 ± 0.0559	0.126 ± 0.0484 [n=4]	0.124 ± 0.0566	0.124 ± 0.0508 [n=16]
$t_{1/2}$ (h)	6.70 ± 2.67	6.67 ± 4.12 [n=4]	6.91 ± 3.88	6.77 ± 3.29 [n=16]
CL/F (L/h)	51.4 ± 16.1	57.9 ± 20.3 [n=4]	42.9 ± 18.9	49.8 ± 18.1 [n=16]
Vz/F (L)	486 ± 261	578 ± 445 [n=4]	440 ± 259	492 ± 296 [n=16]

Notes: AUCs and C_{max} values are presented as geometric mean (geometric CV). T_{max} values are presented as median (minimum, maximum). Other parameters are presented as arithmetic mean ± SD

Milestones:

Final report: 29 November 2022

KVD900-112 summary

Study short name and title:

KVD900-112: A Phase 1, Four-Part, Open-Label, Fixed-Sequence Trial to Evaluate the Effects of Verapamil, Efavirenz, Cimetidine, and Modafinil on the Single-Dose Pharmacokinetics of KVD900 [sebetralstat] in Healthy Adult Participants

Rationale and study objectives:

A previous clinical trial for sebetralstat (KVD900-106; see above) assessed the potential for a drug interaction with a strong CYP3A4 and P-gp inhibitor, itraconazole, and a strong CYP3A4 inducer, phenytoin. The results showed a clinically significant drug-drug interaction.

Overall plasma sebetralstat exposure (based on AUC_{0-t} and AUC_{0-inf}) and peak exposure (based on C_{max}) were 421%, 420%, and 135% higher, respectively (90% CI for AUC_{0-t}: 455%-596%; 90% CI for AUC_{0-inf}: 456%-594%; 90% CI for C_{max}: 193%-287%), when sebetralstat was co-administered with itraconazole versus sebetralstat alone. Given that only a small effect on the PK of sebetralstat was seen in KVD900-106 when sebetralstat was dosed with quinidine (a specific P-gp inhibitor), these results indicate that CYP3A4 inhibition does indeed increase both peak concentrations and exposure to sebetralstat.

Similarly, overall plasma sebetralstat exposure (based on AUC_{0-t} and AUC_{0-inf}) and peak exposure (based on C_{max}) were 84%, 83%, and 66% lower, respectively (90% CI for AUC_{0-t}: 14%-20%; 90% CI for AUC_{0-inf}: 14%-21%; 90% CI for C_{max}: 24%-46%), when sebetralstat was co-administered with phenytoin versus sebetralstat alone. These results indicate that CYP3A4 induction will reduce peak concentrations and sebetralstat exposure. The trial KVD900-106 confirms the *in vitro* results that CYP3A4 enzyme activity is predominantly responsible for sebetralstat metabolism in humans. A further trial (KVD900-112) assessed the PK of sebetralstat with concomitant administration of moderate and weak inhibitors and inducers of CYP3A4.

The trial was designed in four parts. For all trial parts, a washout period of at least 5 days was used between the sebetralstat dose in Period 1 and the (first) dose of interacting drug in Period 2 (i.e., verapamil, efavirenz, cimetidine, or modafinil). This washout was based on the finding in the KVD900-106 trial, whereby there were 4 instances of quantifiable sebetralstat pre-dose concentrations (albeit < 5% of subsequent C_{max} concentration). The washout used in each trial part was considered sufficient to prevent carryover effects between doses of sebetralstat.

Inhibition or induction of CYP enzymes requires a significantly longer washout to return enzyme activity to the baseline level. Therefore, a fixed sequence design was chosen for all trial parts to minimise the washout and overall trial duration.

Study Objectives

Part 1 – Effect of verapamil on sebetralstat

Primary Objective:	To determine the effect of multiple-dose verapamil, a moderate CYP3A4 inhibitor, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of verapamil in healthy adult participants.

Part 2 – Effect of efavirenz on sebetralstat

Primary Objective:	To determine the effect of multiple-dose efavirenz, a moderate CYP3A4 inducer, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of efavirenz in healthy adult participants.

Part 3 – Effect of cimetidine on sebetralstat

Primary Objective:	To determine the effect of single-dose cimetidine, a weak CYP3A4 inhibitor, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with a single dose of cimetidine in healthy adult participants.

Part 4 – Effect of modafinil on sebetralstat

Primary Objective:	To determine the effect of multiple-dose modafinil, a weak CYP3A4 inducer, on the single-dose PK of sebetralstat in healthy adult participants.
Secondary Objective:	To determine the safety and tolerability of a single dose of sebetralstat when administered alone and with multiple doses of modafinil in healthy adult participants.

Study design:

KVD900-112 was a four-part, multiple-period, open-label drug-drug interaction study that evaluated the pharmacokinetics, safety, and tolerability of sebetralstat in the presence of index CYP3A4 perpetrators. A total of 64 healthy male and female subjects were enrolled in this trial. In each part, sebetralstat was assessed as a 'victim' of an enzyme-mediated interaction. Sebetralstat was administered alone, followed by a washout period and then again after administration of a perpetrator to ensure maximal inhibition or induction of the specific pathway. Pharmacokinetic sampling and subject monitoring continued in-clinic through 48 hours after the last dose of sebetralstat.

The metabolic pathway alteration, dosing regimen, and number of subjects enrolled in each part were:

- Part 1 moderate CYP3A4 inhibition: 600 mg of sebetralstat alone (Day 1 of period 1) and then 240 mg verapamil (1 x 240 mg tablet) administered QD for 6 days (Day 1 to Day 6 of period 2) with 600 mg sebetralstat co-administered with verapamil on Day 5, n=16 and n=16; sebetralstat alone and in the presence of the perpetrator, respectively.
- Part 2 moderate CYP3A4 induction: 600 mg of sebetralstat alone (Day 1 of period 1) and then 600 mg efavirenz (1 x 600 mg tablet) administered QD at bedtime for 14 days (Day 1 to Day 14 of period 2) with 600 mg sebetralstat administered on Day 14, n=16 and n=15; sebetralstat alone and in the presence of the perpetrator, respectively.

- Part 3 weak CYP3A4 inhibition: 600 mg of sebetralstat alone (Day 1 of period 1) and then 800 mg cimetidine (4 x 200 mg tablets) co-administered with 600 mg sebetralstat (Day 1 of period 2), n=16 and n=16; sebetralstat alone and in the presence of the perpetrator, respectively.
- Part 4 weak CYP3A4 induction: 600 mg of sebetralstat alone (Day 1 of period 1) and then 200 mg of modafinil (1 x 200 mg tablet) administered QD for 15 days (Day 1 to Day 15 of period 2) with 600 mg sebetralstat co-administered with modafinil on Day 14, n=16 and n=16; sebetralstat alone and in the presence of the perpetrator, respectively.

All parts:

Safety was monitored throughout the trial by repeated clinical and laboratory evaluations.

Discontinued participants could be replaced at the discretion of the Sponsor.

Study population:

Up to 64 participants were to be enrolled in the trial. Sixteen (16) healthy, adult, male and female (of non-childbearing potential) participants were to be enrolled in each study part. Participants would participate in only one part of the trial.

Screening of participants was to occur within 28 days prior to the first dosing.

Study results:

Pharmacokinetic results from this drug-drug interaction study added additional support to suggest sebetralstat is a sensitive substrate of CYP3A4. Sebetralstat exhibited a 102% increase in AUC when administered with a moderate CYP3A4 inhibitor and a 12% decrease when administered with a weak CYP3A4 inhibitor. Sebetralstat exhibited a 79% reduction in AUC when administered with a moderate CYP3A4 inducer and a 21% reduction when administered with a weak CYP3A4 inducer.

In Part 1, the $AUC_{0\text{-}inf}$ and C_{max} of sebetralstat were higher following administration of verapamil, a moderate CYP3A4 inhibitor, compared to sebetralstat alone. Following verapamil plus sebetralstat, the median T_{max} was slightly delayed compared to sebetralstat alone, at 1.25 and 1.13, respectively. The mean T1/2 was slightly longer, and mean CL/F and Vz/F values were lower following verapamil plus sebetralstat relative to sebetralstat alone. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall exposures and peak exposure were 102% and 76% higher, respectively (GMR 90% CI for $AUC_{0\text{-}inf}$: 182.5%-223.9%; GMR 90% CI for C_{max}: 147.0-211.6%), following verapamil plus sebetralstat versus sebetralstat alone. Based on the results, verapamil, a moderate CYP3A4 inhibitor, inhibited sebetralstat metabolism.

In Part 2, the $AUC_{0\text{-}inf}$ and C_{max} of sebetralstat were lower following administration of efavirenz, a moderate CYP3A4 inducer, compared to sebetralstat alone. Following efavirenz plus sebetralstat, the median T_{max} (1.00 hours) was slightly earlier relative to sebetralstat alone (1.13 hours). The mean T1/2 was shorter (4.49 hours) following efavirenz plus sebetralstat compared to sebetralstat alone (6.51 hours). The mean Vz/F and CL/F values were higher following co-administration with efavirenz relative to sebetralstat alone. The ln-transformed plasma sebetralstat PK parameters demonstrated overall exposures and peak exposures were 79% and 63% lower, respectively (GMR 90% CI for $AUC_{0\text{-}inf}$: 16.8%-25.8%; GMR 90% CI for C_{max}: 28.2%-47.8%) following efavirenz plus sebetralstat versus sebetralstat alone. Based on the results, sebetralstat is sensitive to moderate CYP3A4 inducers.

In Part 3, the $AUC_{0\text{-}inf}$ and C_{max} of sebetralstat were slightly lower following administration of cimetidine, a weak CYP3A4 inhibitor, plus sebetralstat compared to sebetralstat alone. Following cimetidine plus sebetralstat, the median T_{max} occurred earlier relative to sebetralstat alone, 0.75 hours and 1.01 hours, respectively. The mean T1/2 was lower when cimetidine was co-administered with sebetralstat versus sebetralstat alone, 5.53 hours versus 7.34 hours, respectively. Mean CL/F and Vz/F values were higher following cimetidine plus sebetralstat compared to sebetralstat alone. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall and peak exposure were 12% and 22% lower, respectively (GMR 90% CI for $AUC_{0\text{-}inf}$: 73.4%-105%; GMR 90% CI for C_{max}: 63.5%-95.7%), following cimetidine plus sebetralstat relative to sebetralstat alone. Since co-administration of cimetidine (a weak CYP3A4 inhibitor) with sebetralstat resulted in a slight decrease in AUCs and C_{max}, weak inhibition of CYP3A4 by cimetidine would be expected to cause an increase in AUC values for a sensitive substrate, suggesting that sebetralstat is not likely a sensitive substrate of cimetidine-inhibited CYP3A4 metabolism.

In part 4, the $AUC_{0\text{-}inf}$ and C_{max} of sebetralstat were slightly lower following administration of modafinil, a mild CYP3A4 inducer, compared to sebetralstat alone. Following modafinil plus sebetralstat, the median T_{max} was earlier relative to sebetralstat alone, at 0.8 and 1.5 hours, respectively. The mean T1/2 was slightly shorter, and the mean CL/F was slightly larger following modafinil plus sebetralstat relative to sebetralstat alone. Mean Vz/F values were similar among the treatments. The statistical comparisons of ln-transformed plasma sebetralstat PK parameters demonstrated overall and peak exposure were 21% and 11% lower, respectively (GMR 90% CI $AUC_{0\text{-}inf}$: 64.8%-95.4%; GMR 90% CI C_{max}: 63.9%-123.9%), following modafinil plus sebetralstat relative to sebetralstat alone. Following modafinil plus sebetralstat administration, there were minimal decreases in plasma sebetralstat exposures, suggesting minimal sensitivity of sebetralstat to weak induction of CYP3A4 metabolism.

A summary of pharmacokinetic parameters for each of the four parts and summary PK profiles are presented below.

Table SIII-13: KVD900-112: PK Parameters

Sebetralstat in the presence of a moderate CYP3A4 inhibitor (verapamil)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+verapamil (n=16)**	**Geometric Mean Ratio (%) [90%CI]**
C_{max} (ng/mL) mean (min, max)	5,050 (1,420, 14,700)	8,900 (5,160, 19,700)	176.4 [147.0-211.6]
T_{max} (h) median	1.13	1.25	-
T1/2 (h) mean (%CV)	5.95 (67.7)	6.20 (35.2)	
K_{el} (h^{-1}) mean (%CV)	0.116 (67.7)	0.112 (35.2)	
CL/F (L/h) mean (%CV)	30.5 (40.0)	15.1 (29.6)	
V_z/F (L) mean (%CV)	262 (113)	135 (57.4)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	19,700 (11,400, 43,300)	39,800 (24,000, 72,500)	202.2 [182.5-223.9]
Sebetralstat in the presence of a moderate CYP3A4 inducer (efavirenz)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+efavirenz (n=15)**	**Geometric Mean Ratio (%) [90%CI]**
C_{max} (ng/mL) mean (min, max)	4,760 (974, 9,560)	1,740 (229, 4,490)	36.7 [28.2-47.8]
T_{max} (h) median	1.13	1.00	-
T1/2 (h) mean (%CV)	6.51 (52.6)	4.49 (67.6)	
K_{el} (h^{-1}) mean (%CV)	0.107 (52.6)	0.154 (67.6)	
CL/F (L/h) mean (%CV)	32.2 (38.2)	156 (60.5)	
V_z/F (L) mean (%CV)	302 (78.2)	1,010 (101)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	18,600 (8,140, 36,000)	3,840 (1,420, 9,650)	20.8 [16.8-25.8]
Sebetralstat in the presence of a weak CYP3A4 inhibitor (cimetidine)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+cimetidine (n=16)**	**Geometric Mean Ratio (%) [90%CI]**
C_{max} (ng/mL) mean (min, max)	5,380 (2,450, 10,800)	4,190 (1,890, 8,670)	77.9 [63.5-95.7]
T_{max} (h) median	1.01	0.75	-
T1/2 (h) mean (%CV)	6.7 (47.5)	9.22 (47.3)	
K_{el} (h^{-1}) mean (%CV)	0.104 (47.5)	0.0751 (47.3)	
CL/F (L/h) mean (%CV)	28.6 (29.0)	32.6 (33.6)	
V_z/F (L) mean (%CV)	275 (68.2)	434 (51.1)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	20,900 (11,300, 32,400)	18,400 (8,980, 29,600)	87.8 [73.4-105.0]

Sebetralstat in the presence of a weak CYP3A4 inducer (modafinil)			
Pharmacokinetic Parameter (n)	**Sebetralstat Alone (n=16)**	**Sebetralstat+modafinil (n=15)**	**Geometric Mean Ratio (%) [90%CI]**
C_{max} (ng/mL) mean (min, max)	4,740 (1,490, 9,400)	4,200 (1,280, 11,600)	89.0 [63.9-123.9]
T_{max} (h) median	1.50	0.77	-
T1/2 (h) mean (%CV)	7.34 (51.9)	5.53 (45.7)	
K_{el} (h^{-1}) mean (%CV)	0.0945 (51.9)	0.125 (45.7)	
CL/F (L/h) mean (%CV)	31.7 (40.3)	41.0 (54.0)	
V_z/F (L) mean (%CV)	336 (92.6)	327 (87.1)	
$AUC_{0\text{-}inf}$ (h•ng/mL) mean (min, max)	18,900 (8,450, 29,500)	14,600 (5,280, 31,900)	78.6 [64.8-95.4]

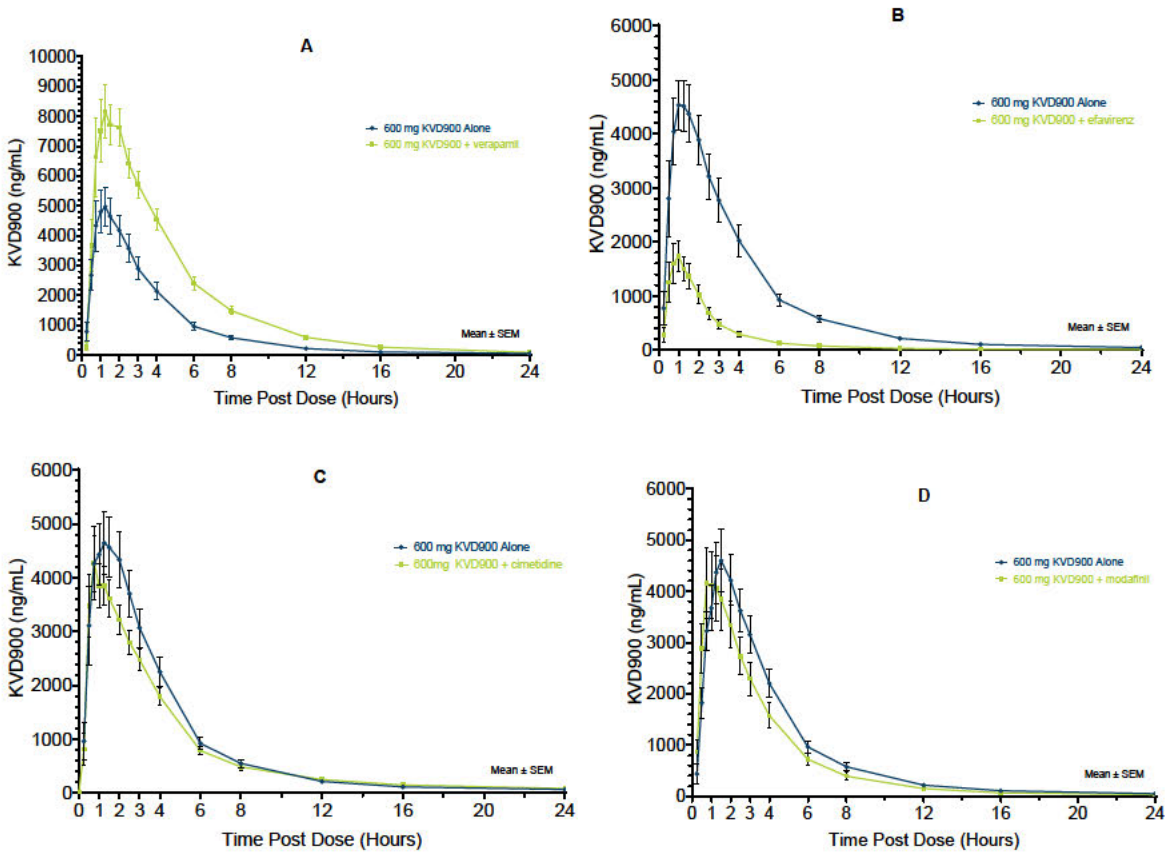

Figure III-1: KVD900-112: Sebetralstat (KVD900) Plasma Concentrations Over Time After Sebetralstat Alone and After Co-Administration with A) verapamil, B) efavirenz, C) cimetidine, and D) modafinil. Data presented as Mean (arithmetic)

Milestones:

Final report: 02 October 2023

SIII.3 Phase 2 Clinical Trials

A single Phase 2 clinical trial (KVD900-201) examined the safety, efficacy, pharmacokinetic and pharmacodynamic impact of sebetralstat 600 mg in the on-demand treatment of angioedema attacks in adult (aged 18 to 68 years) participants with HAE Type I or II.

The study was conducted in two parts:

Part 1 investigated the safety, pharmacokinetics and PD of open-label sebetralstat during the period between HAE attacks.

Part 2 was a randomised, double-blind, placebo-controlled, 2-way cross-over trial that investigated the efficacy of sebetralstat. Participants were randomised into one of two treatment sequences. One participant received a single dose of sebetralstat 600 mg in the treatment sequence to treat the first eligible HAE attack. Following the resolution of this attack, participants received a single dose of placebo to treat the second eligible HAE attack. In treatment sequences, participants received a single dose of a placebo to treat the first eligible HAE attack. Following the resolution of this attack, participants received a single dose of sebetralstat 600 mg to treat the second eligible HAE attack.

Sixty-eight participants were randomised, and 53 completed the study drug administration for two attacks. Fourteen participants did not complete their second attack, including one who could not complete their final visit and one who withdrew consent. One hundred twenty-six doses of sebetralstat were administered: 68 during Part 1 of the study and 58 during Part 2.

Study results:

Sebetralstat was rapidly absorbed following oral administration, with measurable concentrations detected within 0.25 hours. Plasma levels of sebetralstat quickly achieved maximum values (geometric mean C_{max}: 6,080 ng/mL) with an observed median T_{max} of 1.00 hour (range: 0.433 to 3.00 hours).

A review of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $AUC_{\%extrapolated}$ values indicated that most of the exposure following a single oral dose of 600 mg sebetralstat was accounted for in the period up to 12 hours post-dose as illustrated by a geometric mean $AUC_{\%extrapolated}$ of less than 20%.

Table SIII-14: KVD900-201: Summary of Derived Plasma Sebetralstat PK Parameters

Treatment	Summary Statistic	Cmax (ng/mL)	Tmax (h)	AUC0-t (h•ng/mL)	AUC0-inf (h•ng/mL)	AUC%extrap. (%)	Kel (/h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
600 mg Sebetralstat (N=42)	n	42	42	42	30	30	30	30	30	30
	Mean	6,570	1.20	13,700	18,800	21.2	0.471	1.56	36.6	80.6
	Geometric Mean	6,080	N/A	12,900	17,600	19.6	0.457	1.52	34.0	74.5
	SD	2,650	0.677	4,720	6,780	7.89	0.124	0.371	15.4	39.1
	CV%	40.3	56.3	34.5	36.0	37.2	26.2	23.8	42.2	48.5
	Minimum	2,600	0.433	4,700	6,350	6.89	0.269	0.935	18.0	43.1
	Median	6,370	1.00	12,700	17,000	23.3	0.424	1.64	35.4	66.3
	Maximum	13,600	3.00	25,600	33,400	45.4	0.742	2.58	94.4	241

Milestones:

Final report: 16 November 2021

SIII.4 Phase 3 Clinical Trials

The following are the pivotal studies supporting the safety and efficacy of sebetralstat (note: this list may expand/change during development based on dialogue with Health Authorities).

Table SIII-15: Phase 3 Clinical Trials

Study Identifier	Study Type
KVD900-301	A Phase 3 efficacy study. Randomised, double-blind, placebo-controlled, cross-over study to evaluate the efficacy and safety of sebetralstat in the treatment of HAE attacks
KVD900-302	A Phase 3, open-label, long-term safety study of sebetralstat in the treatment of HAE attacks

KVD900-301 Summary

Study name and title:

KVD900-301: A Randomised, Double-Blind, Placebo-Controlled, Phase 3, Three-way Cross-over Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900 [sebetralstat], 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)

Rationale and study objectives:

Recurrent swelling in patients with HAE is predominantly due to excessive bradykinin generation due to dysregulated plasma kallikrein activity. Therefore, inhibition of plasma kallikrein activation has emerged as a target for treating HAE.

Sebetralstat has been shown in a range of nonclinical experiments to be a selective inhibitor of plasma kallikrein. It is, therefore, a plausible hypothesis that treatment with a single dose of sebetralstat 600 mg may halt the progression of HAE attacks.

This hypothesis was tested in a Phase 2 trial (KVD900-201) for the on-demand treatment of HAE attacks. The trial was a cross-over in which 53 patients with either Type I or II HAE completed. Results showed a significant difference between sebetralstat 600 mg and placebo for the primary endpoint of time to conventional treatment use and secondary endpoints of attack improvement using Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S), and a composite visual analogue scale (VAS) measuring symptoms of the attack.

Primary Objective: To demonstrate the clinical efficacy of sebetralstat compared with placebo for the on-demand treatment of HAE attacks.

Secondary Objective: To investigate the safety and tolerability of sebetralstat.

Study design:

KVD900-301 was a Phase 3, double-blind, randomised, placebo-controlled, multicentre clinical trial in patients aged 12 years or older with HAE Type I or II. Patients were randomly assigned to 6 treatment sequences in a 3-way crossover design. Eligible attacks were to be treated with a single dose of placebo, 300 mg sebetralstat, or 600 mg sebetralstat per attack with a minimum 48-hour washout period between each eligible attack and the last dose of IMP or conventional on-demand treatment. If needed (as determined by the patient), a second dose of IMP would be administered for each attack.

The estimated duration of this trial for each randomised patient was approximately 25 weeks from screening through the final visit, and it included treating 3 eligible attacks during the treatment period.

This trial was conducted at HAE treatment centres on an outpatient basis and comprised in-clinic and televisits. A televisit may have been conducted via a telephone call or an interactive audio/video system. If an in-clinic visit could not be undertaken (e.g. in the event of the COVID-19 pandemic or other reason that prevented the patient from attending the in-clinic visit), home health visits were to be used, if permitted by the relevant regulatory authority, the site's EC/IRB, local regulations, and the patient via informed consent. The home visit was to be performed by an appropriately delegated home healthcare service provider. Information captured during a home health visit was to mirror that captured in an in-clinic visit.

Study population:

A total of 136 patients were randomly assigned to receive the IMP, of which 110 patients treated at least one attack with IMP and, therefore, were included in the FAS and Safety Set, and 86 patients were included in the per-protocol set (PPS). Of the 110 patients included in the FAS and Safety Set, this included 13 adolescent patients that were evaluable for the primary analysis.

Sixty-eight (61.8%) of the 110 patients in the FAS and Safety Set completed the trial, and 42 (38.2%) did not. Those who did not complete the trial were primarily discontinued due to the specified overall number of attacks for trial completion being reached, and, therefore, ongoing patients were discontinued. The sponsor recorded these discontinuations as trial termination in the EDC (32 [29.1%] patients). All 110 patients treated their first attack with IMP, 86 patients treated their second attack with IMP, and 68 patients treated their third attack with IMP for a total of 264 treated attacks.

The median age of the patients in the Safety Set was 39.5 years and ranged from 13 to 74 years. This included 13 adolescent (aged 13-17 years) and 97 adult (aged 18-74 years) patients. More females were enrolled than males (60% versus 40%). Most patients enrolled were White (92 [83.6%] patients) by race and non-Hispanic or Latino (95 [86.4%] patients) by ethnicity. The mean weight was 77.86 kg (range: 41 to 140.3 kgs), and the mean BMI was 27.44 kg/m^2.

Most patients had HAE Type 1 (101/110 [91.8%] patients); 90/110 [81.8%] patients had a primary relative with HAE. The mean time since HAE diagnosis was 14.850 years. The mean time since the last attack before randomisation was 41.02 days.

Study results:

A total of 264 attacks were treated and included in the FAS. The baseline characteristics of the treated attacks included all attack severities (none to very severe) and locations (abdominal,

subcutaneous, laryngeal, and mixed). Baseline characteristics for IMP-treated attacks were similar across the treatment groups.

Most 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 the 300 mg sebetralstat group [range: 6.0 to 130], 41 minutes for the 600 mg sebetralstat group [range: 5.0 to 142], and 51 minutes for the placebo group [range: 6.0 to 166]).

Most primary pooled attack locations were subcutaneous 142 [53.8%] and abdominal only 85 [32.2%]. The laryngeal swelling occurred in 8 [3.0%] of the attacks.

In the Safety Set, most attacks were treated with 1 dose of IMP; the rate was higher in the sebetralstat treatment groups compared with the placebo group: 53 [61.6%] attacks in the 300 mg sebetralstat group, 56 [58.9%] attacks in the 600 mg sebetralstat group versus 37 [44.6%] attacks in the placebo group. Where a second dose was taken, the median time between the 2 IMP doses was 3.858 hours for the 300 mg sebetralstat group, 3.783 hours for the 600 mg sebetralstat group, and 3.500 hours for the placebo group.

Efficacy Results

Primary endpoint

There was a statistically significant improvement in the time to the beginning of symptom relief between 300 mg sebetralstat (adjusted p<0.0001) versus placebo group and between 600 mg sebetralstat (adjusted p=0.0013) versus placebo group. The median (95% CI) time to the beginning of symptom relief was 1.61 hours (95% CI: 1.28, 2.27) for the 300 mg sebetralstat group, 1.79 hours (95% CI: 1.33, 2.27) for the 600 mg sebetralstat group, and 6.72 hours (95% CI: 2.33, not evaluable) for the placebo group. More attacks reached the beginning of symptom relief within 12 hours of the first IMP administration in the sebetralstat treatment groups than in the placebo group (300 mg sebetralstat group: 66 [75.9%] attacks and 600 mg sebetralstat group: 71 [76.3%] attacks versus placebo group: 41 [48.8%] attacks).

Key Secondary endpoints

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

There was a statistically significant improvement in the complete HAE attack resolution between the 300 mg sebetralstat group (adjusted p=0.0022) versus the placebo group and the 600 mg sebetralstat group (adjusted p<0.0001) versus the placebo group. The median (95% CI) time to complete HAE attack resolution was not evaluable (95% CI: 16.60, not evaluable) for the 300 mg sebetralstat group, 24.00 hours (95% CI: 10.6, not evaluable) for the 600 mg sebetralstat group, and not evaluable, i.e., >24 hours for the placebo group. More attacks reached complete HAE attack resolution within 24 hours of the first IMP administration in the 300 mg sebetralstat

(37 [42.5%] attacks) and 600 mg sebetralstat groups (46 [49.5%] attacks) than in the placebo group (23 [27.4%] attacks).

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

Safety Results

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

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

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

The majority of TEAEs were mild (24 events) or moderate (37 events) in severity; 1 severe event was reported (intervertebral disc protrusion for 1 patient in the 300 mg sebetralstat group; this event was also an SAE).

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

None of the TEAEs resulted in IMP discontinuation, trial discontinuation or death. Three SAEs were reported in 3 (2.7%) patients: intervertebral disc protrusion in 1 patient in the 300 mg sebetralstat group and anisocoria and hereditary angioedema (reported term: HAE exacerbation) in 1 patient each in the 600 mg sebetralstat group. All 3 SAEs led to hospitalisation. The SAE in the 300 mg sebetralstat group was also reported as a Grade 3 (severe) AE. None of the SAEs were considered to be related to the IMP.

No clinically significant trends were observed in mean values after baseline through the end of the trial in the laboratory safety parameters, vital signs, or ECG parameters. Physical examination assessments were reported to be normal, not clinically significant in the majority of the patients and abnormal, not clinically significant at final/ET visit in a few patients, except for 3 patients whose assessments [body systems: neurological, extremities, general appearance, and dermatological] were reported to be abnormal, clinically significant.

Conclusions

This double-blind, placebo-controlled trial enrolled a broad HAE population of patients aged 12 and older who were using long-term prophylactic or only on-demand treatment. The protocol encouraged patients to treat their attacks per current treatment guidelines. Accordingly, all attack severities and locations were eligible for treatment as soon as possible after onset.

The efficacy of sebetralstat compared with the placebo was consistently demonstrated using multiple outcome measures. The primary and key secondary endpoints in this trial were all met. A statistically significant and clinically meaningful improvement was observed in the results of the primary and key secondary endpoints (time to the beginning of symptom relief, time to reduction in severity, and complete HAE attack resolution) for attacks treated with 300 mg or 600 mg sebetralstat compared with placebo. Efficacy results were consistent with the overall population across all subgroups analysed, for example, baseline attack severity, initial attack location, use of long-term prophylactic treatment, and age of the patient. The secondary efficacy endpoints were consistent and supportive of the primary and key secondary endpoints at both sebetralstat dose levels.

Sebetralstat was safe and well tolerated at both doses in adult and adolescent patients 12 years and older.

<u>Milestones:</u>

Final report: 03 May 2024

KVD900-302 Summary

Study short name and title:

KVD900-302: An Open-label Extension Trial to Evaluate the Long-term Safety of KVD900 [sebetralstat], 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-S)

Rationale and study objectives:

Sebetralstat is a potent inhibitor of plasma kallikrein, as shown in plasma samples from completed Phase 1 and Phase 2 trials of sebetralstat in healthy volunteers (KVD900-101) and participants with Type I or II HAE (KVD900-201) at dose levels up to 600 mg. The clinical efficacy of 2 dose levels of sebetralstat was investigated in a Phase 3 trial, KVD900-301, a double-blind, randomised, placebo-controlled, multicentre clinical trial in patients 12 years of age or older with HAE Type I or II. The patients were randomised to 6 treatment sequences in a 3-way crossover design. Eligible attacks were treated with a placebo, 300 mg or 600 mg sebetralstat per attack (with the option for patients to take a second dose of sebetralstat to treat each attack) with a minimum 48-hour washout period between attacks.

The current trial, KVD900-302, is an open-label, multicentre extension trial to evaluate the long-term safety of 600 mg sebetralstat in patients 12 years of age or older with HAE Type I or II. Long-term efficacy is also being evaluated as a secondary objective.

Primary Objective:	To assess the safety of long-term administration of sebetralstat in adolescent and adult patients with HAE type I or II.
Secondary Objectives:	To investigate the safety and tolerability of sebetralstat.
	To assess the long-term efficacy of sebetralstat in treating attacks in adolescent and adult patients with HAE type I or II.
	To assess the safety and efficacy of sebetralstat when used as short-term prophylaxis in adolescent and adult patients with HAE types I or II.

Study design:

KVD900-302 is an open-label, multicentre extension trial to evaluate the long-term safety of sebetralstat in patients 12 years of age or older with HAE type I or II. This trial will be conducted on an outpatient basis and includes in-clinic or home health visits and ‘televisits’.

The maximum duration of this trial for individual patients is two years.

Study population:

HAE treatment centres worldwide will enrol approximately 150 patients with HAE type I or II (including a minimum of 12 adolescents).

The population will include rollover and non-rollover patients. Rollover patients are defined as patients who were randomised in the KVD900-301 trial. Non-rollover patients include all other patients. Non-rollover patients enrolled at a site participating in the KVD900-301 efficacy trial must have Sponsor approval before enrolling in this long-term safety trial.

At the time of data cut-off for this interim analysis (31 January 2024), a total of 118 patients had been screened: 68 rollover patients from the KVD900-301 and 50 non-rollover patients (including 2 patients previously randomly assigned in the KVD900-201 trial). Five (4.2%) patients, all non-rollover, failed screening.

Of the 113 patients who were enrolled, 84 patients received at least 1 dose of the IMP after an HAE attack and were included in the Safety Set and FAS. Five patients were included in the STP-SAF, and 2 patients were in the PKS.

Seven (8.3%) patients discontinued the trial. The primary reasons for discontinuations were withdrawal by patient (4 [4.8%] patients) and AEs (3 [3.6%] patients). A total of 77 (91.7%) patients are ongoing in the trial.

The patients' mean (SD) age was 35.9 (15.49) years, ranging from 13 to 77 years. The majority (72 [85.7%] patients) were ≥18 years of age. There were 54 (64.3%) female and 30 (35.7%) male patients. Most of the patients were White by race (63 [75.0%] patients) and not Hispanic or Latino (69 [82.1%] patients) by ethnicity. The mean (SD) body mass index (BMI) was 26.86 (6.122) kg/m^2. The demographic characteristics were well-balanced between the rollover and non-rollover patients.

Interim study results:

Efficacy Results

Sebetralstat showed consistent efficacy, with comparable results between rollover and non-rollover patients and with repeated treatment (Attack 1 to Attack 18).

Overall efficacy results showed the following: The time to the beginning of symptom relief within 12 hours was achieved for most HAE attacks (475 of 639 attacks [74.3%]). The median time to the beginning of symptom relief was 1.8 hours (95% CI: 1.77, 1.96), showed consistency with repeated treatment, and was consistent between rollover and non-rollover patients.

51.6% of HAE attacks were reduced in severity within 12 hours. The median time to reduction in severity was 6.57 hours (95% CI: 5.02, 8.82), and it was consistent with repeated treatment and between rollover and non-rollover patients.

59.1% of HAE attacks resolved completely within 24 hours of the first IMP administration. The median time to complete attack resolution was 21.02 hours (95% CI: 18.55, 21.50), and it was consistent with repeated treatment and between rollover and non-rollover patients.

The frequency of on-demand conventional treatment within 12 and 24 hours was low (5.6% and 8.4% of the attacks, respectively); thus, the median time to conventional on-demand treatment use within 12 and 24 hours could not be calculated. The use of conventional on-demand treatment was consistent with repeated treatment and was consistent between the rollover and non-rollover patients.

Total and domain AE-QoL scores varied from Month 1 to Month 10 but were comparable to baseline. The clinical significance of these results will be reported in the final report when more patients have been observed for longer.

The final report will summarise and analyse baseline HAE attack characteristics.

Of the 5 patients who used STP, none experienced an HAE attack within 24 hours following IMP administration.

Safety Results

Sebetralstat was well tolerated with a favourable safety profile after repeated administration. There was no clinically significant difference in the safety profile between rollover and non-rollover patients.

Of the 84 patients in the Safety Set, 47 (56.0%) reported 153 TEAEs. Eight (9.5%) patients reported 18 TEAEs related to the IMP.

Twenty-six (31.0%) patients reported a TEAE within 3 days of IMP administration (on-treatment). On-treatment TEAEs were either of mild or moderate severity.

Four (4.8%) patients reported a TEAE that led to trial discontinuation, and two (2.4%) patients reported two on-treatment TEAEs leading to trial discontinuation.

One (20.0%) patient reported 2 TEAEs after STP.

Five (6.0%) patients reported 6 TEAEs of Grade 3 severity, of which only 1 TEAE (diarrhoea) was related to the IMP.

The most commonly reported TEAEs by preferred term (PT) (≥2% overall) were headache (10 [11.9%] patients); nasopharyngitis and upper respiratory tract infection (7 [8.3%] patients each); COVID-19 and viral upper respiratory tract infection (4 [4.8%] patients each); vomiting, influenza, and urinary tract infection (3 [3.6%] patients each); and diarrhoea, seasonal allergy, gastroenteritis, gastroenteritis viral, alanine aminotransferase increased, aspartate aminotransferase increased, back pain, migraine, urticaria (all reported by 2 [2.4%] patients each).

The most common TEAE related to the IMP was headache (3 [3.6%] patients reporting 4 TEAEs). All other TEAEs related to IMP were reported by 1 (1.2%) patient each. All IMP-related TEAEs were either mild or moderate in severity, except for 1 severe TEAE (diarrhoea) reported by 1 patient. Three (3.6%) patients reported 5 serious TEAEs (hyperthermia, meningitis viral, Waldenström's macroglobulinemia, headache, and intracranial mass). None of the reported serious TEAEs were IMP-related. There were no TEAEs leading to death in the trial.

No clinically relevant changes, shifts, or trends were observed in laboratory parameters from baseline to post-baseline timepoints, and no pregnancies were reported.

Abnormal post-baseline laboratory parameters reported as TEAEs were only reported in one patient (who presented with an abnormal ALT and AST and abnormal GGT).

Other safety findings showed minor post-baseline fluctuations in vital signs (systolic and diastolic blood pressure, respiratory rate, pulse rate) that were not considered clinically significant. No clinically significant changes were reported in other baseline vital signs.

Six patients had clinically significant physical examination findings; all findings were reported as TEAEs or associated with an HAE attack.

Pharmacokinetic Results

An ongoing separate PK sub-trial in adolescent patients, which 2 adolescent patients have completed to date, showed that the results were similar to the modelled results for each adolescent patient.

At 0.5 to 2 hours, the mean (SD) plasma concentration of SEBETRALSTAT was 1625.00 (2156.676) ng/mL; at 2- to 4-hours, it was 2890.00 (1781.909) ng/mL; and at 4- to 6-hours, it was 5810.00 (6208.398) ng/mL. The 4- to 6-hour plasma concentrations were impacted as one patient took the second IMP dose before the sample collection.

Conclusions

Sebetralstat was safe and well tolerated in patients aged 12 years and older for long-term treatment of HAE attacks. This was consistent in both rollover and non-rollover patients.

The results for all efficacy endpoints from this trial were consistent with the Phase 3 pivotal study (KVD900-301). Efficacy was consistent with repeated treatment and in both rollover and non-rollover patients.

Milestones:

Interim report: 03 May 2024 (Data cut-off date: 31 January 2024)

SIII.5 Clinical Pharmacokinetics

In Phase 1 studies, 411 adult male and female volunteers received sebetralstat. Concentrations of sebetralstat reach maximal plasma levels rapidly, with the median T_{max} in each study being approximately 1 hour or shorter under fasted conditions. When administered with a high-fat, high-calorie breakfast, the median T_{max} was delayed by 2 hours. The observed delay to median T_{max} in the fed state (Food and Drug Administration [FDA] high-fat breakfast within 30 minutes of dosing) is consistent with delayed gastric emptying in the presence of food. The $t_{½}$ of sebetralstat increased with increasing doses as a longer and more robust elimination phase became evident (e.g., from 6 to 13 hours after 160 to 600 mg single doses, respectively).

Sebetralstat has been assessed in two DDI trials, which indicated that sebetralstat is a sensitive substrate of CYP3A4; BCRP or P-gp transporter inhibition had only a minor effect on the PK of sebetralstat. In a hepatic impairment trial in patients with mild and moderate hepatic impairment, study results indicated that moderate hepatic impairment impacted the PK of sebetralstat.

Sixty-eight patients with HAE Type I or Type II received sebetralstat in Part 1 of the Phase 2 trial. There were no meaningful differences in the PK or PD profiles in patients with HAE versus that in healthy volunteers.

SIII.6 Clinical Safety

Adverse events were collected and coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) in the individual studies. AEs were summarised according to the System Organ Class (SOC), Preferred Term (PT), and overall levels. At each summary level, a participant was counted once for each reported AE within each level, regardless of whether the AE occurred multiple times. TEAEs were defined with an onset date and time after the initial dose of sebetralstat, index perpetrator, or placebo or if the AE increased in intensity after the initial dose of sebetralstat, index perpetrator, or placebo.

This section presents safety results from all trials completed in the clinical development program and interim safety results from the ongoing open-label trial as of the data cut-off date of 31 January 2024.

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

Across the clinical development program, 6 patients or subjects in the 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) (see table below).

One of the TEAEs leading to trial discontinuation in KVD900-302 was also an SAE (intracranial mass, considered not related to IMP). Two TEAEs leading to trial discontinuation in KVD900-302 occurred on-treatment (i.e. within 3 days after IMP administration) and were considered by the investigator to be related to the IMP (events of skin burning sensation and nausea); both of these events resolved without intervention. The remaining TEAE leading to trial discontinuation in KVD900-302 was an “ALT increased” event subsequent to an SAE of viral meningitis; the event was considered unrelated to the IMP. The 2 TEAEs (AST increased, related; and COVID-19, not related) that occurred in Phase 1 were mild in severity and resolved without intervention.

Table SIII-16: Treatment-Emergent Adverse Events (TEAEs) Leading to Trial Discontinuation or Withdrawal of the IMP, Patients in any Sebetralstat Treatment Group

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

Across the clinical development program, 6 patients reported a total of 8 treatment-emergent SAEs (see table below). None occurred within 3 days after IMP administration (i.e. were not considered on-treatment). None were assessed as related to IMP.

Table SIII-17: Treatment-emergent Serious Adverse Events

Trial	MedDRA SOC/PT	Treatment	Severity/ Causality	Outcome	On-treatment
KVD900-301	Congenital, familial and genetic disorders/ HAE[a]	600 mg	Moderate/ Not related	Recovered/ Resolved	No
KVD900-301	Eye disorders/ Anisocoria	600 mg	Moderate/ Not related	Not recovered/ Not resolved	No
KVD900-301	Musculoskeletal and connective tissue disorders/ Intervertebral disc protrusion	300 mg	Severe/ Not related	Recovered/ Resolved	No
KVD900-302	Infections and infestations/ Meningitis viral	600 mg	Severe/ Not related	Recovered/ Resolved	No
KVD900-302	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)/ Waldenstrom's macroglobulinaemia	600 mg	Moderate/ Not related	Recovering/ Resolving	No
KVD900-302	Nervous system disorders/ Intracranial mass[b]	600 mg	Moderate/ Not related	Not recovered/ Not resolved	No
	General disorders and administration site conditions/ Hyperthermia		Mild/ Not related	Recovered/ Resolved	No
	Nervous system disorders/ Headache		Mild/ Not related	Recovered/ Resolved	No

[a]Verbatim term: HAE exacerbation. [b]The SAE of intracranial mass led to trial discontinuation.

In the Phase 1 Non-DDI trials, which includes both uncontrolled and placebo-controlled trials, TEAEs were reported for 8 (18.2%) subjects who received <300 mg (8 total events), 1 (3.8%) subject who received 300 mg (1 event), 29 (22.7%) subjects who received 600 mg or equivalent (50 total events), 15 (17.9%) subjects who received >600 mg (27 total events), and 10 (13.5%) subjects who received placebo (13 total events) (see table below).

TEAEs considered by the investigator to be related to the IMP were reported for 4 (9.1%) subjects who received <300 mg (4 total events), 1 (3.8%) subject who received 300 mg (1 event), 20 (15.6%) subjects who received 600 mg or equivalent (39 total events), 15 (17.9%) subjects who received >600 mg (25 total events), and 7 (9.5%) subjects who received placebo (10 total events).

No SAEs, Grade 3 or higher TEAEs, or TEAEs leading to trial discontinuation were reported in the Phase 1 Non-DDI trials.

Table SIII-18: Phase 1 non-DDI Safety Population: Summary of Overall Adverse Events

Category	Statistic	Sebetralstat <300 mg (N=44)	Sebetralstat 300 mg (N=26)	Sebetralstat 600 mg or equivalent (N=128)	Sebetralstat >600 mg (N=84)	Placebo (N=74)
Any TEAE	No. (%) of subjects and events	8 (18.2) 8	1 (3.8) 1	29 (22.7) 50	15 (17.9) 27	10 (13.5) 13
Any Related TEAE	No. (%) of subjects and events	4 (9.1) 4	1 (3.8) 1	20 (15.6) 39	15 (17.9) 25	7 (9.5) 10
Any Serious TEAE	No. (%) of subjects and events	0	0	0	0	0
Any Grade 3 or Higher TEAE	No. (%) of subjects and events	0	0	0	0	0
Any TEAE Leading to Trial Discontinuation	No. (%) of subjects and events	0	0	0	0	0

Notes: The Phase 1 Non-DDI Safety Population includes all treated subjects from Phase 1 trials KVD900-101, KVD900-102, KVD900-103, KVD900-104, KVD900-107, KVD900-108, KVD900-109, and KVD900-110. Severe AEs were defined as TEAEs that were classified as severe or life-threatening (Grade 3 or higher) by the investigator.

In the Phase 2 and 3 Double-Blind trials, 17 (19.8%) patients who received 300 mg sebetralstat reported a total of 20 TEAEs; 28 (18.5%) patients who received 600 mg KVD900 reported a total of 39 TEAEs, and 24 (17.4%) patients who received placebo reported a total of 34 TEAEs (see table below).

TEAEs considered by the investigator to be related to the IMP were reported for 2 (2.3%) patients who received 300 mg (2 total events), 6 (4.0%) patients who received 600 mg (7 total events), and 6 (4.3%) patients who received placebo (7 total events).

One (1.2%) patient who received 300 mg and 2 (1.3%) patients who received 600 mg reported SAEs: no SAEs were considered related to the IMP. The SAE (1.2%) reported for the patient who received 300 mg was Grade 3 in severity.

There were no TEAEs leading to trial discontinuation in KVD900-201 or KVD900-301.

Table SIII-19: Phase 1 non-DDI Safety Population: Summary of Overall Adverse Events

Number of participants with:	Statistic	Sebetralstat 300 mg (N=86)	Sebetralstat 600 mg (N=151)	Placebo (N=138)
Total Person-Time (Years)	No. (%) of patients and events	15.37	24.64	20.25
Any TEAE	No. (%) of patients and events	17 (19.8) 20	28 (18.5) 39	24 (17.4) 34
Any Related TEAE	No. (%) of patients and events	2 (2.3) 2	6 (4.0) 7	6 (4.3) 7
Any Serious TEAE	No. (%) of patients and events	1 (1.2) 1	2 (1.3) 2	0
Any Serious Related TEAE	No. (%) of patients and events	0	0	0
Any Grade 3 or Higher TEAE	No. (%) of patients and events	1 (1.2) 1	0	0
Any Related Grade 3 or Higher TEAE	No. (%) of patients and events	0	0	0
Any TEAE Leading to Trial Discontinuation	No. (%) of patients and events	0	0	0

Notes: The Phase 2 and 3 Double-blind Safety Population included all randomised and treated patients from Phase 2 and 3 trials KVD900-201 and KVD900-301, respectively, during the double-blind treatment period. Severe AEs were defined as TEAEs that were classified as severe or life-threatening (Grade 3 or higher) by the investigator.

Overall, the type and frequency of TEAEs were similar following treatment with KVD900 compared with placebo. When the controlled Phase 2 and 3 trials were combined, the only TEAE reported by ≥2% of patients in any treatment group was headache (1 [1.2%] patient who received 300 mg, 7 [4.6%] patients who received 600 mg, and 4 [2.9%] patients who received placebo). Of those TEAEs, only 2 in both the 600 mg and placebo groups were assessed as related (2 [1.3%] and 2[1.4%], respectively).

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

From the KVD900-301 trial individually, adverse reactions are defined as TEAEs deemed related to KVD900, occurring within 3 days of dosing with KVD900 (i.e., on-treatment). Adverse reactions observed in ≥1% of patients in any KVD900 treatment group that also occurred at a higher rate than placebo are summarised in Table SIII.20; adverse reactions meeting this criterion are dyspepsia and fatigue.

Table SIII-20: Adverse Reactions Observed In ≥1% of Patients in any Sebetralstat Treatment Group and at a Higher Rate than Placebo in KVD900-301 (Safety Set)

Adverse Reaction	Placebo (N=83) n (%)	Sebetralstat	
		300 mg (N=86[a]) n (%)	600 mg (N=93[a]) n (%)
Dyspepsia	0	1 (1.2)	0
Fatigue	0	1 (1.2)	0

[a]No. of attacks treated in the group.

SIII.7 Summary

Sebetralstat (also referred to as KVD900) is a novel small molecule inhibitor of human plasma kallikrein (PKa) that has been developed as an oral treatment for hereditary angioedema (HAE) attacks in adults and children aged 12 years and older. Pharmacodynamic data from nonclinical (in vitro) and clinical studies (ex vivo) have shown that, 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.

In addition, sebetralstat also directly halts the FXII to FXIIa feedback loop, further reducing the amount of plasma kallikrein available. Compared to C1-INH (*in vitro*), as used in some of the current HAE treatments, sebetralstat demonstrated a faster response onset and equivalent or better potency.

In the studies conducted to date, sebetralstat has been generally safe and well tolerated in healthy volunteers and patients with HAEF. There have been no clear patterns or discernible trends in AEs following treatment with sebetralstat or placebo.

Part II: Module SIV - Populations not Studied in Clinical Trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Key exclusion criteria for the majority of completed clinical studies are presented in the table below.

Table SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Any concomitant diagnosis of another form of chronic/recurrent angioedema.	To better assess the effect of sebetralstat on the subject and specifically on HAE.	No	Concurrent diagnosis of other forms of chronic/recurrent angioedema may distort, mask or influence study results and their interpretation.
Past medical history of poor response to bradykinin receptor 2 blocker, C1-INH, factor XIIa inhibitor, or PKa inhibitor in the opinion of the study Investigator.	Likely poor response to treatment with other treatments with a similar mechanism of action.	No	Previous poor response to these therapies suggests a predictable poor response to sebetralstat.
Use of C1-INH, androgens, berotralstat, lanadelumab or tranexamic acid for HA (in Phase 3 studies, only androgens and tranexamic acid are prohibited).	Exclusion of other forms of HAE treatment that may impact study results.	No	Other HAE therapies may distort, mask or influence study results and their interpretation.
Use of angiotensin-converting enzyme (ACE) inhibitors.	ACE inhibitors may distort, mask or influence study results and their interpretation.	No	ACE inhibitors modulate the kallikrein-kinin system.
Use of any oestrogen-containing medications with systemic absorption (such as oral contraceptives including ethinyl-oestradiol or hormone replacement therapy [HRT]).	Oestrogen-containing medications with systemic absorption may distort, mask or influence study results and their interpretation.	No	Oestrogen has the potential to impact kallikrein expression/regulation.
Use of strong CYP3A4 inhibitors and inducers during study participation.	Avoidance of potentially altered sebetralstat levels and the potential distortion of study results.	No	Sebetralstat is metabolised predominantly by CYP3A4. Concomitant administration of strong and moderate CYP3A4 inhibitors/inducers will likely alter sebetralstat exposure.
Clinically significant abnormal electrocardiogram (ECG) at study entry/initial visits.	Requirement for baseline normal ECG at study entry.	No	Study subject safety. Baseline normal ECG at study entry also allows for better detection, assessment and investigation of any subsequent ECG abnormalities

Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular abnormality.	Requirement for baseline healthy cardiovascular status at study entry.	No	Study subject safety. Baseline healthy cardiovascular status at study entry also allows for better detection, assessment and investigation of any subsequently arising cardiovascular pathology.
Any clinically significant comorbidity or systemic dysfunction, which, in the opinion of the study Investigator, would jeopardise the patient's safety should they participate in a trial.	Requirement for baseline healthy subjects at study entry.	No	Study subject safety. Baseline healthy subjects at study entry also allow for better detection, assessment, and investigation of any subsequently arising pathology.
Impaired hepatic function	No dose adjustment is required for patients with mild hepatic impairment. It is recommended to use Ekterly cautiously in subjects with moderate hepatic impairment. In patients with moderate hepatic impairment who are taking a strong CYP3A4 inhibitor a single dose of 300 mg is recommended when treating an HAE attack. The use of sebetralstat in patients with severe hepatic impairment is not recommended.	No	Study subject safety. Phase 1 trial KVD900-104 indicated moderate hepatic impairment will likely increase sebetralstat exposure, but no dose adjustment is required. Use in severe hepatic impairment should be avoided. Severe hepatic impairment patient will not be treated and therefore not considered as a missing information.
Known hypersensitivity to sebetralstat or placebo or any of the excipients.	Avoidance of predictable hypersensitivity reactions.	No	Study subject safety. Avoidance of predictable hypersensitivity reactions.
History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the study Investigator.	Substance abuse/dependent individuals are unlikely to make reliable study subjects.	No	Unreliable study subjects.
Participation in an interventional investigational clinical study within a specified period before initial study treatment.	Study subject safety. To avoid previous treatments impacting study results and impairing assessment of any adverse events.	No	To ensure that no effects of previous investigational treatments impact study results or potential adverse events.
Participation in any gene therapy treatment or trial for HAE.	Study subject safety. To avoid previous treatments impacting study results and impairing assessment of any adverse events.	No	To ensure that no effects of previous investigational treatments impact study results or potential adverse events.
Any pregnant or breastfeeding patient.	Population excluded from the clinical development program. Sebetralstat is not recommended for pregnant women, and the relative risk should be weighed when considering taking sebetralstat while breastfeeding.	Yes	The effect of sebetralstat on the unborn foetus and on breastfeeding infants is unknown.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical trial development program is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Post-marketing safety monitoring will support the identification of these reactions.

SIV.3 Limitations Concerning Populations Typically Under-Represented In Clinical Trial Development Programs

Table SIV-2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with hepatic impairment were studied in the Phase 1 study KVD900-104. The results indicated that sebetralstat systemic exposure was comparable in mild hepatic impairment and normal hepatic function groups. Subjects with moderate hepatic impairment, however, showed higher systemic exposures than subjects with normal hepatic function, indicating that moderate hepatic impairment had an impact on the PK of sebetralstat. However, given the proposed clinical dose, indication for use/administration, rapid onset of action and clearance, and considering the degree of PK impact, no dose adjustment is required for patients with either mild or moderate hepatic impairment. It is recommended to use Ekterly cautiously in subjects with moderate hepatic impairment Use of Ekterly in patients with severe hepatic impairment (Child-Pugh C) is not recommended.
• Patients with renal impairment	Patients who had estimated glomerular filtration rate (eGFR) ≤90 mL/min/1.73m^2 were not excluded from participating in trials; 19.5% of patients enrolled across the phase 1-3 trials had an eGFR less than or equal to that rate. There have been no clinical renal safety findings considered related to the IMP in healthy subjects or patients with HAE, including reduced eGFR.
• Patients with cardiovascular impairment	Not included in the clinical development program
• Immunocompromised patients	Not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program

Type of Special Population	Exposure
Population with relevant different ethnic origin	Patients with different ethnic origins were studied in the Phase 1 study KVD900-110 to Evaluate the safety, tolerability, pharmacokinetics, and PD of sebetralstat FCTs in Healthy Adult Caucasian, Chinese, and Japanese Volunteers. The results were as follows: Following single doses of 300 mg, 600 mg, and 1,200 mg sebetralstat, plasma concentrations exhibited high variability for most time points. Following single doses of 300 mg to 1,200 mg, the median T_{max} ranged from 0.64 hours to 1.29 hours post-dose, which did not appear to be dose-dependent and was comparable across all ethnic populations. Following single doses of 300 mg to 1,200 mg, the arithmetic mean T1/2 of sebetralstat was 3.492 hours–6.912 hours, comparable across ethnic populations. The mean C_{max} following a single dose of sebetralstat 300 mg was 3,511 ng/mL and 3,173 ng/mL in Japanese and Chinese participants, respectively. This was higher compared to Caucasian participants (2,490 ng/mL); however, there was substantial overlap between the groups. The C_{max} following a single dose of 600 mg was comparable between the ethnic groups (means 6,375 ng/mL–6,777 ng/mL). Following a single 1,200 mg dose, the mean C_{max} was 10,390 ng/mL and 9,292 ng/mL in Japanese and Chinese participants, respectively, and this was higher compared to Caucasian participants (5,997 ng/mL). However, there was substantial overlap between the groups. Sebetralstat mean of $AUC_{0\text{-}inf}$ ranged from 7,882 h•ng/mL-8,352 h•ng/mL, and 17,050 h•ng/mL–18,980 h•ng/mL following single doses of 300 mg and 600 mg, respectively, and there was no apparent difference between the ethnic populations. Following a 1,200 mg dose of sebetralstat, the mean $AUC_{0\text{-}inf}$ was 33,410 h•ng/mL in Chinese participants and was considered higher compared to Japanese (23,020 h•ng/mL) and Caucasian (25,740 h•ng/mL) participants. However, there was substantial overlap between the groups.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other • Children • Elderly (65 years of age or older)	 The safety and efficacy of sebetralstat in children under 12 years of age has not yet been established. No data are available. Ten geriatric patients (aged ≥65 years) (1.5% of the All-Subjects Safety Population) participated in clinical trials, including 4 subjects (0.9%) in Phase 1 trials and 6 patients (2.3%) in Phase 2-3 trials (of whom 5 received sebetralstat).

Part II: Module SV - Post-authorisation Experience

Not applicable (pre-Marketing Authorisation).

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No formal drug dependency studies of sebetralstat have been conducted but based on its pharmacokinetics and pharmacology as a PKa inhibitor, there is no theoretical reason to expect that sebetralstat will be misused for illegal purposes.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

There are no identified risks considered important for inclusion in the list of safety concerns in the initial submission of the RMP (RMP version 1.1, March 2025), which is reflected in the table below.

Table SVII-1: Safety Concerns in the Initial RMP

Important identified risks	None
Important potential risks	None
Missing information	None

SVII.1.1 Risks not Considered Important for Inclusion in the List Of Safety Concerns In the RMP

In the pre-clinical and clinical studies conducted to date, sebetralstat has been generally safe and well tolerated in healthy volunteers and patients with HAE Type I or II. There have been no clear patterns or discernible trends in AEs following treatment with sebetralstat or placebo.

SVII.1.2 Risks Considered Important for Inclusion in the List Of Safety Concerns In the RMP

No important identified risks, important potential risks, or missing information are included in the list of safety concerns in the sebetralstat RMP, which is reflected in the table below.

Table SVII-2: Risks Considered Important for Inclusion in the List Of Safety Concerns in the RMP

Risk type	Risk-benefit impact
Important identified risks	
None	Not applicable
Important potential risks	
None	Not applicable
Missing information	
None	Not applicable

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation Of Important Identified Risks And Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

No important identified risks, important potential risks, or missing information are included in the list of safety concerns in the sebetralstat RMP, which is reflected in the table below.

Table SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities for sebetralstat include:

- Collection, recording, and assessment of individual case safety reports (ICSRs), including expedited reporting of suspected adverse reactions to the relevant regulatory authorities.
- Periodic signal detection activities and evaluation to identify any new safety information.
- Submission of periodic safety update reports (PSURs) per EU regulations to provide a cumulative analysis of safety data.
- Continuous monitoring of pharmacovigilance data within the company's risk management system to ensure the product's benefit-risk balance remains favourable.

These routine activities are in compliance with EU Good Pharmacovigilance Practices (GVP) guidelines and are sufficient to ensure the safety of sebetralstat.

III.2 Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are planned for sebetralstat. This decision 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.

No safety studies are imposed as a condition of the marketing authorisation (category 1), as specific obligations in the context of a marketing authorisation under exceptional circumstances or conditional marketing authorisation (studies category 2), or required by the Competent Authority (category 3).

A tabulated summary of ongoing/completed pharmacovigilance study protocols is provided in [redacted].

III.3 Summary Table of Additional Pharmacovigilance Activities

The Competent Authority has not imposed any ongoing or planned additional pharmacovigilance activities.

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities, which are conditions of the marketing authorisation				
None ongoing or planned	-	-	-	-
Category 2 – Imposed mandatory additional pharmacovigilance activities, which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None ongoing or planned	-	-	-	-

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
None ongoing or planned	-	-	-	-

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

Risk minimisation measures aim to ensure the safe and effective use of sebetralstat by addressing safety concerns identified in the RMP. As no important identified risks, important potential risks, or missing information are included in the list of safety concerns for sebetralstat, therefore routine risk minimisation measures are considered sufficient. No additional risk minimisation measures are required.

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures for sebetralstat are implemented through the Product Information, including the Summary of Product Characteristics (SmPC) and the Package Leaflet (PL). These provide comprehensive information to Health Care Providers (HCPs) and patients to support the safe and effective use of the product.

Key elements of the routine risk minimisation measures for sebetralstat include:

The Summary of Product Characteristics

- Recommendations for dosing adjustments when sebetralstat is co-administered with strong or moderate CYP3A4 inducers to mitigate the risk of suboptimal exposure.
- Clear guidance on using sebetralstat appropriately, including indications, contraindications, warnings, and precautions.

The Package Leaflet

- Patient-friendly explanations of the proper use of sebetralstat and potential interactions with other medicines.

Table Part V-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional 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.

V.3 Summary of Risk Minimisation Measures

The safety profile of sebetralstat, as established during clinical development, does not require measures beyond routine risk minimisation activities. These measures include:

- Clear, evidence-based recommendations in the sebetralstat Product Information (SmPC and PL) to support appropriate use.
- Regular pharmacovigilance activities to monitor and ensure safe and effective use of sebetralstat.

Routine risk minimisation measures are considered sufficient to maintain a favourable benefit-risk balance for sebetralstat.

Table Part V-2: Summary Table Of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not applicable

Part VI: Summary of the Risk Management Plan for Ekterly

Summary of the risk management plan for Ekterly (sebetralstat)

This is a summary of the risk management plan (RMP) for Ekterly (sebetralstat). The RMP details important risks of Ekterly, how these risks can be minimised, and how more information will be obtained about Ekterly's risks and uncertainties (missing information).

Ekterly's summary of product characteristics (SmPC) and its package leaflet give healthcare professionals and patients essential information on how Ekterly should be used.

This summary of the RMP for Ekterly should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ekterly's RMP.

I. The medicine and what it is used for

Ekterly is authorised for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older (see SmPC for the full indication). It contains sebetralstat as the active substance, and it is given orally.

Further information about the evaluation of Ekterly's benefits can be found in Ekterly's EPAR, including in its plain-language summary, available on the EMA website under the medicine's webpage European Public Assessment Reports (EPARs).

II. Risks associated with Ekterly and activities to minimise or further characterise the risks

Important risks of Ekterly, together with measures to minimise such risks and the proposed studies for learning more about Ekterly's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ekterly is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ekterly are risks that need special risk management activities to investigate further or minimise the risk so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ekterly. Potential risks are concerns for which an association with this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

There are no important identified risks, important potential risks, or missing information that are considered important for inclusion in the list of safety concerns in the Ekterly RMP.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Ekterly.

II.C.2 Other studies in the post-authorisation development plan

There are no studies required for Ekterly.

Part VII: Annexes

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[redacted]

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

[redacted]

Annex 6: Details of Proposed Additional Risk Minimisation Activities (If applicable)

Not applicable.

Annex 7: Other Supporting Data (Including referenced material)

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