drugs and drug candidates

MDPI

*Review*

# Sebetralstat: A Rapidly Acting Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema

**Edward P. Feener [1,*], Rebecca L. Davie [2], Nivetha Murugesan [1], Stephen J. Pethen [2], Sally L. Hampton [2], Michael D. Smith [1], Paul K. Audhya [1] and Chris M. Yea [2]**

[1] KalVista Pharmaceuticals, Cambridge, MA 02142, USA; nim@kalvista.com (N.M.); mds@kalvista.com (M.D.S.); pka@kalvista.com (P.K.A.)
[2] KalVista Pharmaceuticals, Porton Down SP4 0BF, UK; rld@kalvista.com (R.L.D.); sjp@kalvista.com (S.J.P.); slh@kalvista.com (S.L.H.); cmy@kalvista.com (C.M.Y.)
* Correspondence: epf@kalvista.com

**Abstract:** Sebetralstat is a novel, potent, and selective oral plasma kallikrein inhibitor drug candidate in clinical development for the on-demand treatment of hereditary angioedema (HAE). Upon binding, sebetralstat induces a conformational change in the active site of plasma kallikrein, which contributes to its high potency ($K_i$ 3 nM) and selectivity (>1500 fold) against other serine proteases. Its physiochemical properties promote both rapid dissolution in the stomach and rapid absorption in the upper intestine that contribute to its fast and efficient absorption. A single oral administration of sebetralstat rapidly provides near-complete inhibition of plasma kallikrein and blockade of high-molecular-weight kininogen cleavage as early as 15 min, which drives its clinical efficacy. In a phase 2 clinical trial, sebetralstat significantly reduced the time to beginning of symptom relief ($p < 0.0001$) with median times of 1.6 h (95% CI: 1.5–3.0) with sebetralstat versus 9.0 h (4.0–17.2) with placebo. KONFIDENT (NCT05259917) is a phase 3 clinical trial assessing the on-demand use of sebetralstat for HAE. If successful, this trial could support the approval of sebetralstat as the first noninvasive, on-demand treatment option to rapidly halt HAE attacks and provide fast symptom relief.

**Keywords:** plasma kallikrein; hereditary angioedema; kallikrein kinin system; bradykinin; oral treatment; plasma kallikrein inhibitor; sebetralstat

check for updates

**Citation:** Feener, E.P.; Davie, R.L.; Murugesan, N.; Pethen, S.J.; Hampton, S.L.; Smith, M.D.; Audhya, P.K.; Yea, C.M. Sebetralstat: A Rapidly Acting Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema. *Drugs Drug Candidates* **2024**, *3*, 328–341. https://doi.org/10.3390/ddc3020019

Academic Editor: François Marceau

Received: 22 February 2024
Revised: 29 March 2024
Accepted: 1 April 2024
Published: 7 April 2024

**Correction Statement:** This article has been republished with a minor change. The change does not affect the scientific content of the article and further details are available within the backmatter of the website version of this article.

**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

## 1. Role of Plasma Kallikrein in Hereditary Angioedema

Hereditary angioedema (HAE) is a rare genetic disease that causes episodic swelling in the skin and submucosal membranes [1]. The anatomical location and severity of attacks, which can occur in the face, extremities, abdomen, genitalia, oropharyngeal tissues, or larynx, is often unpredictable [2]. Attacks that cause airway obstruction can be life-threatening [3]. Criteria for the diagnosis of HAE include the clinical presentation of recurrent subcutaneous or submucosal angioedema that lasts more than 12 h and/or unexplained recurrent abdominal pain that spontaneously resolves in 24–72 h, and laboratory measurements of C1 inhibitor demonstrating a <50% deficiency [1]. Additional information that supports diagnosis include a documented family history of HAE and the identification of C1 inhibitor gene mutations that affect its synthesis or function. Inadequate control of the plasma kallikrein kinin system (KKS) has been identified as the underlying disease mechanism responsible for HAE attacks [4,5].

### *1.1. Plasma Kallikrein-Mediated HAE Attacks*

HAE attacks are mediated by increased vascular permeability caused by the KKS [4,6]. Plasma kallikrein (PKa), a trypsin-like serine protease, cleaves high-molecular-weight kininogen (HK) to generate the nonapeptide hormone bradykinin and cleaved HK (cHK), which can serve as a marker for KKS activation [7]. Bradykinin activates B2 receptors that are ubiquitously expressed and influence an array of vascular, immune, and neuronal

cellular functions [8,9]. The activation of B2 receptors in the vasculature can have a variety of effects, including vasorelaxation, blood pressure decrease, and increased vascular permeability [9,10]. PKa also cleaves Factor XII (FXII) to generate the serine protease FXIIa that converts plasma prekallikrein to PKa. This positive feedback mechanism of the KKS amplifies the generation of PKa and bradykinin-mediated edema and inflammation. Thus, PKa activity is responsible for both the production of bradykinin and amplification of KKS activation.

The interaction of FXII with negatively charged surfaces or activating enzymes leads to the generation of both FXIIa and PKa, which mediate the positive feedback mechanism of KKS amplification in blood and affected tissues. The activity of the KKS is normally controlled by C1 inhibitor (C1INH, encoded by the *SERPING1* gene), the primary physiological inhibitor of both PKa and FXIIa [11]. Mutations in the *SERPING1* gene that result in reduced C1INH expression (HAE Type I) or impaired function (HAE Type II) are the primary causes of HAE (termed HAE-C1INH). Insufficient C1INH levels or function facilitate uncontrolled PKa activity, resulting in increased concentrations of bradykinin. This leads to the extravasation of fluid into the affected tissue, which results in swelling and pain [4]. The prevalence of HAE-C1INH has been estimated to be approximately 1:50,000 in the US [12]. HAE can also occur in the presence of normal levels of C1INH protein and function (termed HAE-nC1INH). The causes of HAE-nC1INH are heterogenous and not fully understood. Although genetic information and therapeutic responses from a limited number of studies have implicated the KKS in attacks in people with HAE-nC1INH [13–15], the underlying etiology for most individuals with a presumptive diagnosis of HAE-nC1INH has not been elucidated. The prevalence of HAE-nC1INH in the US was recently estimated to be about 1200 [16].

### *1.2. PKa Inhibitors Used for the Treatment of HAE*

#### 1.2.1. On-Demand Treatments

PKa inhibitors are approved for both the on-demand and prophylactic treatment of HAE. The first selective PKa inhibitor used for the treatment of HAE was ecallantide, a potent, specific, and reversible PKa inhibitor [17,18]. In EDEMA-4, a phase 3 study in 96 patients with HAE-C1INH, the improvement from baseline in the mean symptom complex severity score 4 h after dosing was significantly greater with ecallantide versus a placebo ($-0.8$ vs. $-0.4$; $p = 0.01$) [19]. Although ecallantide provides fast symptom relief during HAE attacks, it is a small recombinant protein that is associated with a risk of anaphylaxis (~4% in clinical trials) and requires subcutaneous administration in the presence of health care professionals (HCPs) trained in the treatment of anaphylaxis. The mechanism of anaphylaxis with ecallantide is not fully understood [20], and anaphylaxis is not associated with other approved PKa inhibitors. The U.S. Food and Drug Administration's (FDA) black box warning for ecallantide indicates that it should only be administered by an HCP with appropriate medical support to manage anaphylaxis and HAE [18,21,22]. This requirement for HCP administration introduces delay in treatment administration following the patient's recognition of attack onset, and is, therefore, primarily used as a rescue therapy. Increased PKa inhibition can also be achieved by restoring C1INH function using either plasma-derived or human recombinant C1INH. While the exogenous administration of C1INH is effective for the treatment of HAE attacks, only the intravenous application of C1INH is available for on-demand treatment [22], which also increases treatment burden and delays.

Most of the effects of PKa on vascular permeability have been attributed to the bradykinin-mediated activation of B2 receptors. The subcutaneous administration of icatibant, a B2 receptor antagonist, is approved for the on-demand treatment of HAE attacks [23]. In FAST-3, a phase 3 study in patients with HAE-C1INH, median time to 50% or more reduction in symptom severity was 2.0 h with icatibant vs. 19.8 h with placebo ($p < 0.001$) for cutaneous or abdominal attacks [24]. However, nearly all participants in the controlled and open-label extension phases of FAST-3 experienced injection site reactions, including

erythema (overall incidence, 89.2–98.2%; severe, 5.4–19.4%) and swelling (overall incidence, 75.7–86.4%; severe, 1.4–8.1%) [25]. The most common injection site adverse drug reactions for icatibant reported in the FDA Adverse Event Reporting System are site pain, site erythema, and site swelling [26]. Maurer and Church (2012) have demonstrated that subcutaneous injection of icatibant in healthy volunteers induced flares and wheals; these responses were somewhat ameliorated in individuals pretreated with cetirizine [27]. In 2015, McNeil et al. demonstrated that icatibant activates mast cells via the MRGPRX2 receptor [28]. The negatively charged surface in the ligand-binding sub-pocket of the MRGPRX2 receptor has been implicated in its preference for cationic peptidic agonists such as icatibant [29,30]. These findings suggest that icatibant-mediated activation of MRGPRX2 may contribute to its pseudo-allergic injection site reactions, including erythema and swelling [31,32].

#### 1.2.2. Prophylactic Treatments

Two PKa inhibitors are approved for the prophylactic management of HAE. Lanadelumab, a monoclonal antibody that binds and thereby inhibits PKa, was shown to result in 87% HAE attack reduction; 44% of patients were attack-free in a 26-week phase 3 study [33]. Berotralstat, an orally available PKa inhibitor, has been shown to reduce HAE attacks by 44.3% compared with placebo in a 24-week phase 3 study [34]. Although significant reductions in attack frequency among patients receiving long-term prophylaxis have been reported, most patients continue to have attacks, including those affecting the larynx [35–38].

### *1.3. Unmet Need for On-Demand HAE Therapies*

Current guidelines recommend that all attacks be considered for treatment, that attacks should be treated early, and that patients with HAE always have ready access to on-demand treatment for two attacks given the unpredictable nature of HAE [22,39]. Attacks that are treated early are associated with improved outcomes [40,41]. Although both PKa inhibition with ecallantide and B2 receptor antagonism with icatibant are effective in providing on-demand relief from HAE attack symptoms, these therapies require parental administration and can have adverse side effects that may delay or reduce utilization. Oral therapies that rapidly inhibit the KKS could enhance patient compliance with treatment guidelines. We sought to identify and develop a potent and selective PKa inhibitor that provides the rapid and near-complete inhibition of PKa following oral administration and thereby provides fast symptom relief from HAE attacks.

Rationale for Oral On-Demand Treatment of HAE Attacks with a PKa Inhibitor

- Uncontrolled PKa activity is the source of increased bradykinin in HAE-C1INH.
- PKa inhibition is highly effective for the treatment and prevention of HAE attacks.
- PKa inhibition reduces the generation of PKa via the feedback loop of the contact system, thereby decreasing the expansion and worsening of attacks.
- Oral therapies reduce the barriers to early treatment imposed by parenteral therapies (e.g., need for training, portability issues, injection site reactions).
- Patients prefer oral medications over injectables [42].
- Oral on-demand therapies that rapidly halt attacks may reduce the need for prophylaxis.

## 2. Sebetralstat

Sebetralstat (previously named KVD900) (Figure 1) is a potent, selective, and oral PKa inhibitor that provides near-complete inhibition of circulating PKa as early as 15 min following dosing and is well suited for the on-demand treatment of HAE attacks [43,44]. A summary of sebetralstat's properties is shown in Table 1.

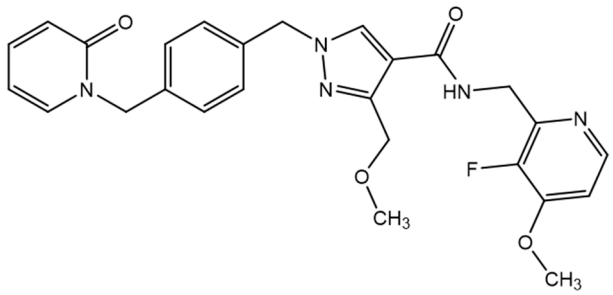



**Figure 1.** Structure of sebetralstat (KVD900).

**Table 1.** Summary of sebetralstat's properties. Reprinted with permission from Ref. [45]. 2022, Rebecca L Davie, Hannah J Edwards, D Michael Evans, Simon T Hodgson, Michael J Stocks, Alun J Smith, Louise J Rushbrooke, Stephen J Pethen, Michael B Roe, David E Clark, Paul A McEwan, Sally L Hampton.

| | | | |
|---|---|---|---|
| Mol. Weight | 491.2 Dal | F rat; dog | 82%; 34% |
| $K_i$ | 3.0 nM | $T_{1/2}$ rat; dog | 1.0 h; 1.0 h |
| Isolated PKa $IC_{50}$ | 6 nM | $T_{max}$ rat; dog | 0.4 h; 0.8 h |
| LLE | 6.4 | $V_{ss}$ rat; dog | 0.50 L; 0.65 L |
| $k_{on}$ | $>10 \times 10^6$ $M^{-1}$ $s^{-1}$ | FaSSGF solubility | >1 mg/mL |
| Whole plasma $IC_{50}$ [a] | 54 nM | FaSSIF solubility | 0.29 mg/mL |
| Selectivity [b] | >1500 fold | CYP450 inhibition [c] | >25 µM |
| PPB, human | 77% | hERG inhibition | >33 µM |

$K_i$, inhibitory constant; LLE, lipophilic ligand efficiency; $k_{on}$, rate of association constant; PPB, plasma protein binding; FaSSGF, simulated fasted-state gastric fluid; FaSSIF, simulated fasted-state intestinal fluid; F (%), fraction of orally administered drug that reaches the circulation; $t_{½}$, half-life; $T_{max}$, time to maximal concentration; $V_{ss}$, volume at steady state; hERG, human ether-a-go-go ion channel. [a] Human plasma containing dextran sulfate. [b] Selectivity against an extended panel of related human serine proteases. [c] A cross seven major cytochrome P450 (CYP450) isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4).

### *2.1. Discovery*

The discovery of sebetralstat was described by Davie et al., 2022 [45]. Historically, development of orally bioavailable PKa inhibitors has proven to be challenging due to the belief that trypsin-like serine proteases required charged, basic P1 groups to form a salt bridge interaction with ASP189 to achieve potent inhibition [46]. The presence of charged, highly basic groups within drugs can be detrimental to absorption, which is required for oral bioavailability [47]. We employed a strategy to reduce the reliance of the charged interaction between ASP 189 and the P1 moiety by reducing the basic $pK_a$ value of the P1 group in a stepwise manner. The optimization of binding interactions in additional pockets of the active site would be required to maintain potent inhibitors. At the project concept stage, most of the reported PKa inhibitors contained a benzamidine or equally basic P1 group ($pK_a$ values between 11 and 12). Hit compound 1 was discovered as a suitable starting point, with 3.7 µM inhibition against PKa and a relatively low molecular weight (Figure 2). The hit compound contained benzylamine with a moderately high basic moiety ($pK_a$ 9.1) but a stepwise improvement from benzamidine. Further reductions in the basicity of the P1 group of compound 1 did not yield potent inhibitors. Modification and optimization to the rest of the hit scaffold produced potent inhibitor 2, which enabled the discovery of P1 groups with further reduced basicity exemplified by compound 3, culminating in an array of neutral (non-ionized) benzyl P1 binders. The structure–activity relationship from the array led to the identification of 4, with a preferred 2,6-difluoro-3-methoxy substitution pattern on the phenyl ring. Absorption, distribution, metabolism, and excretion properties were optimized, first by introducing a methoxymethyl substituent onto the pyrazole core, which led to improved permeability, and then with the introduction of a 2-pyridyl ring in place of the phenyl ring of the P1 group, which reduced lipophilicity and increased solubility, to generate sebetralstat (Figure 2).

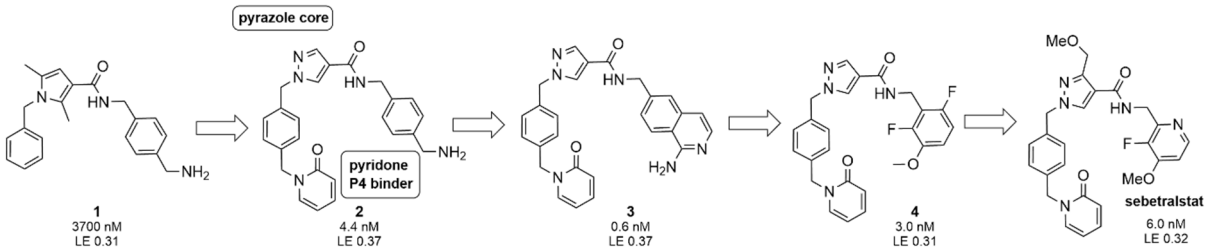



**Figure 2.** Evolution of plasma kallikrein (PKa) inhibitors with reduced basicity in the P1 group. The human PKa $IC_{50}$ and ligand efficiency (LE) for each compound are indicated.

Sebetralstat complexed with PKa (PDB code 8A3Q) adopts a characteristic U-shaped conformation [48] occupying the S1 and induced S4 pocket, as shown in Figure 3A. Conformational change in the protein structure occurs due to the rotation of TRP 215 ("Trp flip") revealing a deep S4 pocket. This movement is accompanied by shifts in both TYR 174 and GLY 99 wherein the benzylpyridone and pyrazole core form a network of π-stacking interactions (TYR 174, TRP 215, and HIS 57), stabilizing the rearrangement. The extended network of hydrogen bonding and π-stacking interactions are shown by dotted lines in Figure 3B. The movement of amino acid residues is shown in Figure 3C using overlays of crystal structures 8A3Q (sebetralstat [green] complexed with PKa [pink]) and 2ANW (benzamidine [yellow] complexed with PKa [gray]). The novel 3-fluoro-4-methoxypyridine P1 group is devoid of specific polar interactions and instead derives favorable binding energy from hydrophobic interactions and displacement of a water molecule close to TYR 228. The conformational change in the protein structure and subsequent stabilization upon binding with sebetralstat likely contributes to both its potency and selectivity.

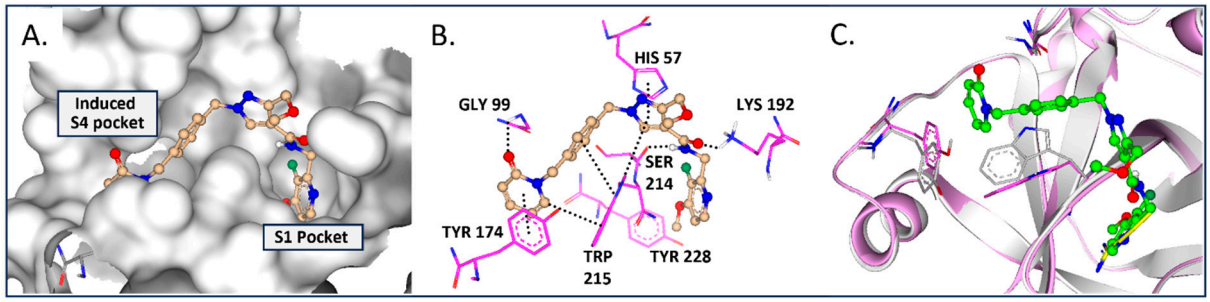



**Figure 3.** (**A**). Crystal structure of sebetralstat complex with PKa (PDB code 8A3Q). (**B**). Key interactions of sebetralstat with residues in the active site of PKa. Network of π-interactions observed: TYR 174/terminal pyridone (face-to-face); TRP 215/phenyl linker (face-to-face) and pyrazole core (edge-to-face); HIS 57/pyrazole core (face-to-face). Hydrogen bonds are observed: GLY 99 backbone N–H/pyridone carbonyl, SER 214 backbone carbonyl/amide N–H, and LYS 192 side chain N–H/amide carbonyl. The pyridine P1 group occupies the S1 subpocket without forming specific polar interactions with any of the amino acids, including ASP 189. (**C**). Overlays of crystal structures 8A3Q (protein shown in pink, sebetralstat in green) and 2ANW (protein in gray, benzamidine in yellow) to highlight the movement of key residues in the S4 region to enable an extended network of π-stacking interactions with sebetralstat. Images created using BioSolvIT SeeSAR v13.0.1; BioSolveIT GmbH, Sankt Augustin, Germany, 2023, www.biosolveit.de/SeeSAR (accessed on 11 December 2023).

### *2.2. Selectivity and Safety Profiling*

The $IC_{50}$ of sebetralstat for human PKa is 6 nM and its selectivity is >1500-fold compared with a panel of related serine proteases (Table 2). Of note, sebetralstat has high selectivity against tissue kallikrein and thus would not be expected to interfere with the generation of Lys-bradykinin, and B2-receptor-mediated actions that may provide beneficial effects in the heart, kidney, and immune system [49,50]. Moreover, the clinical efficacy for HAE attack reduction by a selective blockade of PKa with lanadelumab (as

described above) or donidalorsen (antisense oligonucleotide that inhibits the production of plasma prekallikrein [51]) suggests that tissue kallikrein does not significantly contribute to bradykinin generation that causes HAE attacks [4]. In addition, sebetralstat is selective against FXIa, which shares the highest structural homology to PKa among its closely related serine proteases [52]. Sebetralstat is also selective against other coagulation factors tested, including FXIIa, Fxa, FVIIa, and thrombin.

**Table 2.** Sebetralstat selectivity. $IC_{50}$ values for sebetralstat inhibition of PKa and related proteases in isolated enzyme kinetic fluorogenic substrate assays. Reprinted with permission from Ref. [45]. 2022, Rebecca L Davie, Hannah J Edwards, D Michael Evans, Simon T Hodgson, Michael J Stocks, Alun J Smith, Louise J Rushbrooke, Stephen J Pethen, Michael B Roe, David E Clark, Paul A McEwan, Sally L Hampton.

| Enzyme | $IC_{50}$ |
|---|---|
| Plasma kallikrein | 6.0 nM |
| Tissue kallikrein | >40 µM |
| FXIIa | >40 µM |
| FXIa | >40 µM |
| FXa | >10 µM |
| FVIIa | >10 µM |
| Plasmin | >40 µM |
| Thrombin | >40 µM |
| Trypsin | >40 µM |
| Beta-secretase 1 | >10 µM |
| Cathepsin D | >10 µM |
| Cathepsin G | >10 µM |
| Renin | >10 µM |
| Tissue plasminogen activator | >10 µM |
| Tryptase | >10 µM |

Sebetralstat also displays a high selectivity profile against an off-target safety panel (Eurofins, St. Charles, MO, USA; 124 targets) [45]. No significant inhibition of the hERG channel was observed with sebetralstat at 33 µM (the highest concentration tested) in an electrophysiology patch clamp assay [45]. Sebetralstat has an $IC_{50}$ > 25 µM for the seven major CYP450 isoforms, and multiple CYP450 isoforms contribute significantly to the clearance of sebetralstat, which lowers the risk for CYP-mediated drug–drug interactions [45].

### *2.3. Rapid Absorption following Oral Dosing*

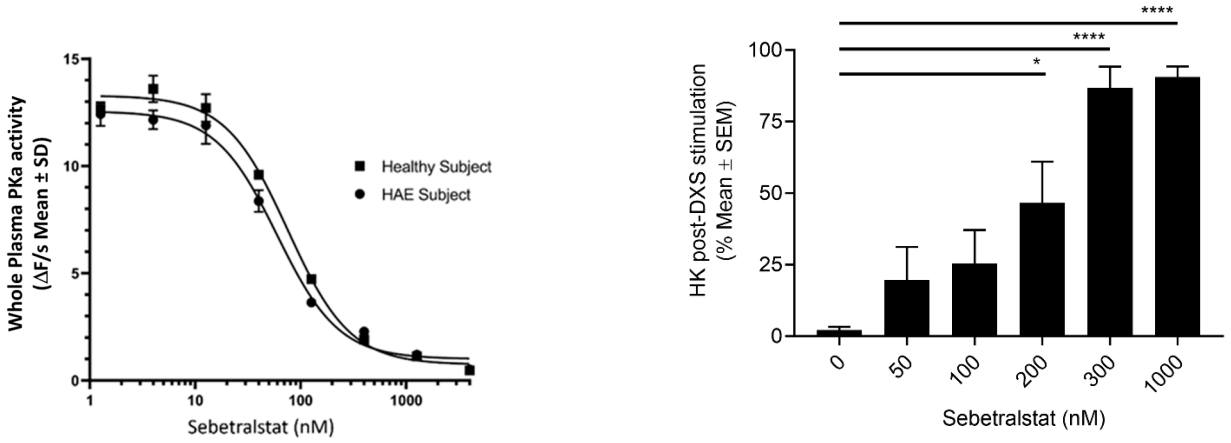
Optimal on-demand treatment of HAE attacks requires fast and near-complete blockade of the KKS. The rapid oral exposure of sebetralstat in a solid tablet formulation is attributed to its rapid dissolution in the stomach followed by its efficient absorption in the upper intestine. The physicochemical characteristics of sebetralstat include a $pK_a$ that is cationic in the stomach (pH 1.5–2.0) due to the protonation of the pyridine nitrogen (measured $pK_a$: 3.6) at gastric pH, yielding a high degree of ionization, enabling a fast dissolution rate and a low degree of ionization in the small intestine (~pH 6.0), enabling efficient absorption. The dissolution of sebetralstat in the stomach is reflected in a high solubility of >1 mg/mL in fasted-state simulated gastric fluid (FaSSGF; pH 1.6), and solubility is maintained at 0.29 mg/mL in fasted-state simulated intestinal fluid (FaSSIF; pH 6.5).

## 3. Sebetralstat In Vitro Pharmacology

Sebetralstat is a competitive and reversible inhibitor of PKa with an estimated $K_i$ of 3.02 ± 0.33 nM (mean ± SD) and $IC_{50}$ for isolated human PKa of 6.0 nM. The association and dissociation kinetics of sebetralstat and PKa are $k_{on} > 10 \times 10^{-6}$ $M^{-1}$ $s^{-1}$ and $k_{off} = 0.0789$ $s^{-1}$, respectively.

The effects of sebetralstat on PKa in whole plasma were analyzed in the presence of dextran sulfate (DXS), which stimulates FXII activation and the generation of PKa. In this whole plasma assay, 6.25 µg/mL of DXS induces a rapid increase in PKa activity with a $V_{max}$ occurring in about 5 min as measured using a fluorogenic substrate. DXS also stimulates cleavage of approximately 60% of the plasma prekallikrein at 17 min,

corresponding to the potential generation of 75–86 nM PKa [44]. This in vitro assay was used to mimic rapid and high-level KKS activation that may occur during an HAE attack. Using this whole plasma assay, sebetralstat has an $IC_{50}$ for PKa in plasma from healthy volunteers of 54.4 nM ± 13.1 (geometric mean ± SD) and from individuals with HAE-C1INH of 47.5 nM ± 10.4 (Figure 4A). The high potency of sebetralstat in DXS-stimulated whole plasma is attributed, in part, to its fast association kinetics for PKa, which was above the limit of detection; $k_{on} > 10 \times 10^{-6}$ $M^{-1}$ $s^{-1}$. The higher $IC_{50}$ in the whole plasma assay compared with the isolated PKa assay was expected based on the high concentration of PKa generated in the former. While the dilution of plasma, which decreases PKa concentration, can lower the apparent PKa inhibitor $IC_{50}$, whole plasma assays likely more closely represent the $IC_{50}$ in vivo.



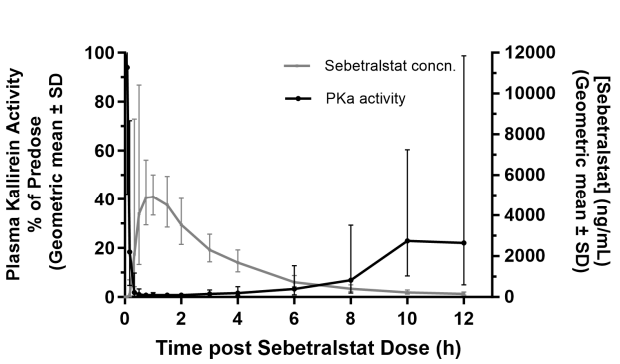

(**A**) (**B**)

**Figure 4.** Dose–response effects of sebetralstat on PKa activity and HK cleavage in human plasma. (**A**) Representative graphs showing dose–response effects of sebetralstat in DXS-stimulated PKa activity in plasma from a healthy volunteer and a patient with HAE-C1INH. (**B**) The percentage of HK after DXS-stimulation of the plasma was determined in the presence or absence of sebetralstat. Bar graph showing the percentage of HK after DXS stimulation compared to HK in unstimulated healthy volunteer plasma (expressed as % mean ± SEM). cHK, cleaved HK; DXS, dextran sulfate; HK, high-molecular-weight kininogen; PKa, plasma kallikrein; SEM, standard error of the mean. *p*-values: **** < 0.0001, * < 0.05. Figure panels (**A**,**B**) were reprinted/adapted with permission from Ref. [44]. 2022 KalVista Pharmaceuticals, Inc. *Clin. Exp. Allergy* 2022, 52, 1059–1070 Duckworth et al. Pharmacological Suppression of the Kallikrein Kinin System with KVD900: An Orally Available Plasma Kallikrein Inhibitor for the On-demand Treatment of Hereditary Angioedema.

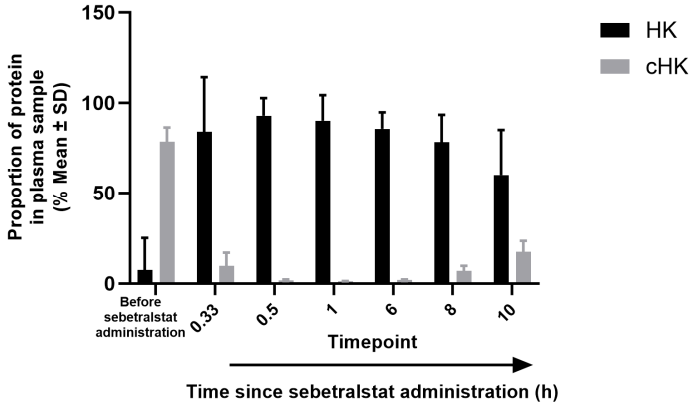
The DXS-stimulated generation of PKa in the whole plasma assay was associated with the near-complete consumption of its endogenous substrate HK in 17 min (Figure 4B). The addition of sebetralstat to plasma protected HK from DXS-stimulated cleavage with an $IC_{50}$ of approximately 200 nM [44]. HK is quantified in an endpoint protein measurement, whereas the whole plasma PKa activity is based on enzyme kinetics ($V_{max}$), which limits the direct comparison of sebetralstat $IC_{50}$ values from these assays.

## 4. Sebetralstat Phase 1 Trials

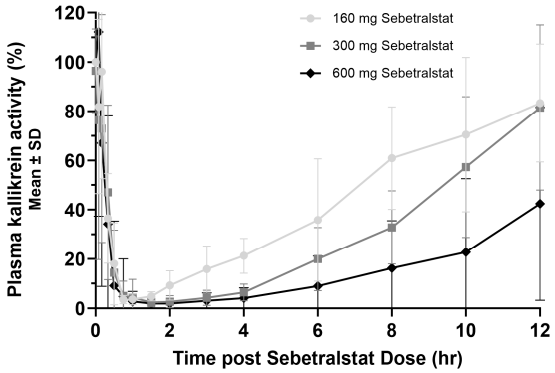
The pharmacodynamics of sebetralstat in healthy adult volunteers was investigated in phase 1 trials [43]. A single dose of 600 mg of sebetralstat in a film-coated tablet formulation was orally administered and plasma was collected predose and at timepoints up to 12 h postdose. Sebetralstat was rapidly absorbed, with a median $T_{max}$ of 0.5 h (range: 0.33–1.5), geomean $C_{max}$ of 6460 ng/mL (CV%: 22.0), and $AUC_{0–24}$ of 18,600 h.ng/mL (CV%: 22.5) (Figure 5A). The oral absorption of sebetralstat was determined as >75% of the dose in a [$^{14}$C] radiolabeled study [53].




(**A**)




(**B**)




(**C**)

**Figure 5.** Effects of sebetralstat on PKa activity and HK cleavage in healthy volunteers. Sebetralstat was administered as a single dose (600-mg tablet) to 12 healthy male volunteers under fasted conditions. Plasma was collected pre- and postdose at the times indicated. (**A**) Sebetralstat concentration in plasma (gray). PKa activity (black) in DXS-stimulated plasma postdose compared with plasma obtained before sebetralstat administration. (**B**) The relative concentration of HK after DXS stimulation as a percentage of total HK and cHK (combined) compared to reference control plasma (arithmetic mean ± SD). (**C**) Population PD data in healthy volunteers administered a single dose of sebetralstat at 160, 300, or 600 mg, and patients with HAE administered a single 600-mg dose. Data show arithmetic mean percent DXS-stimulated PKa activity in plasma samples collected. The indicated timepoints are postdose compared to predose plasma. DXS, dextran sulfate; HK, high-molecular-weight kininogen; cHK, cleaved high-molecular-weight kininogen; SD, standard deviation of the mean. Adapted with permission from Ref. [43]. 2021, Andreas Maetzel, Michael D. Smith, Edward J. Duckworth, Sally L. Hampton, Gian Marco De Donatis, Nivetha Murugesan, Louise J. Rushbrooke, Lily Li, Danielle Francombe, Edward P. Feener, and Christopher M. Yea.

The effects of sebetralstat on both whole plasma PKa activity and HK cleavage were analyzed and compared. At 20 min postdose, DXS-stimulated PKa activity was inhibited by 89.2% (1.9% ± 5.2 HK remaining; mean ± SD), and >90% mean inhibition was observed from 30 min to at least 6 h postdose compared with predose plasma (Figure 5A). The inhibition of mean whole plasma PKa activity by sebetralstat was sustained at >60% for up to 10 h.

The DXS-stimulated generation of cHK in plasma obtained following sebetralstat administration was inhibited by 90.3% (9.7% ± 25.5 HK remaining; mean ± SD) at 20 min postdose and by >98% inhibition of cHK generation from 30 min to 6 h, compared with DXS-stimulated plasma at predose (Figure 5B). Longer-term effects of sebetralstat for HK protection and the inhibition of cHK generation were observed at 8 h (93% inhibition of

cHK) and 10 h (82.4%). As expected, an increased protection of HK inversely correlated with low levels of cHK. In the presence of DXS, inhibition of >90% PKa activity in the whole plasma assay was associated with the near-complete protection of HK cleavage.

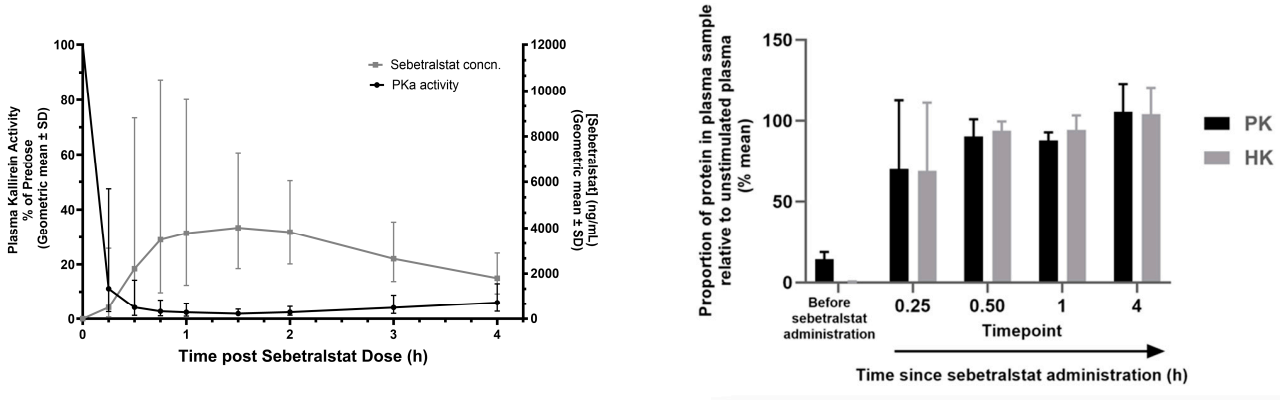
The dose–response effect of 160, 300, and 600 mg of sebetralstat administered as a single dose on PKa activity was examined using population pharmacodynamic data. These results show that all three doses delivered the rapid inhibition of PKa activity and the duration of PKa inhibition was dose-responsive with >90% inhibition maintained for 2 h with 160 mg, 4 h with 300 mg, and 6 h with 600 mg of sebetralstat (Figure 5C).

## 5. Sebetralstat Phase 2 Trials for HAE-C1INH

A single oral dose of 600 mg of sebetralstat was investigated in a phase 2 trial for the on-demand treatment of HAE attacks [54]. Part 1 of the study was open label to assess the safety, pharmacokinetics, and pharmacodynamics of sebetralstat in participants with HAE. Part 2 was a randomized, double-blind, placebo-controlled, two-sequence, two-period ($2 \times 2$) crossover trial. Patients with HAE-C1INH were randomly assigned to receive either a single dose of 600 mg of sebetralstat to treat the first eligible attack and a single dose of a placebo to treat the second eligible attack or a placebo to treat the first eligible attack and 600 mg of sebetralstat to treat the second eligible attack.

In part 1, 68 participants received 600 mg of sebetralstat; plasma samples were collected in 42 participants predose and from 15 min to 4 h postdose. Sebetralstat was rapidly absorbed with a mean 4016 ng/mL $C_{max}$ and 1.5 h $T_{max}$ (geometric mean, $n = 42$). The effects of sebetralstat on DXS-stimulated PKa activity in whole plasma were measured using samples from 26 participants, which had sufficient quantity and quality of plasma samples for all timepoints. The inhibition of PKa activity in plasma obtained at 15 min was 88.9%, and an inhibition of >90% was observed from 30 min to 4 h postdose (latest timepoint assessed, Figure 6). HK and plasma prekallikrein were measured by immunoassay in samples from a randomly selected cohort of six participants with HAE. The protection of both PK and HK from DXS-stimulated cleavage was observed in plasma obtained 15 min after the sebetralstat dose, and the near-complete inhibition of DXS-stimulated HK and prekallikrein cleavage occurred from 30 min to 4 h postdose (the last timepoint analyzed). The rapid inhibition of PKa and protection of HK with sebetralstat in HAE plasma (Figure 6) were similar to the responses observed in healthy plasma (Figure 5). In addition, the protection of prekallikrein from DXS-stimulated cleavage in the presence of sebetralstat suggests a strong inhibition of the positive feedback loop of the contact system. Similar results were shown in the phase 1 trial where sebetralstat inhibited the DXS-stimulated generation of PKa and FXIIa, in addition to protecting HK from cleavage [43].

In part 2, the safety and efficacy of 600 mg of sebetralstat and a placebo were investigated in 68 patients with HAE. The primary endpoint of the trial, time to use of conventional attack treatment within 12 h of study drug administration, was met ($p = 0.001$) with sebetralstat versus the placebo (at quartile 1: >12 h [95% CI: 9.6 to >12] vs. 8.0 h [3.8 to >12]). The time to beginning of symptom relief was defined as at least "a little better" for two consecutive timepoints using the Patient Global Impression of Change (Figure 7). The median time to beginning of symptom relief was 1.6 h (95% CI: 1.5–3.0) with sebetralstat versus 9.0 h (4.0–17.2) with the placebo ($p < 0.0001$) [51]. Moreover, at 12 and 24 h after study drug administration, a greater proportion of attacks treated with sebetralstat were rated at least "a little better" for two consecutive timepoints (44 [83%] at 12 h and 45 [85%] at 24 h) compared with attacks treated with a placebo (27 [51%] at 12 h and 34 [64%] at 24 h; $p = 0.0018$ at 12 h and $p = 0.031$ at 24 h) [54]. In the phase 2 trial of sebetralstat in patients with HAE, there were no serious adverse events or adverse-event-related discontinuations.




(**A**) (**B**)

**Figure 6.** Pharmacokinetic and pharmacodynamic effects of a single oral administration of 600 mg of sebetralstat in a tablet formulation on plasma in participants with HAE-C1INH. Plasma was obtained predose and at the indicated times after sebetralstat administration up to 4 h, the final timepoint measured. (**A**) Mean plasma concentrations of sebetralstat for participants with HAE-C1INH ($n$ = 68 dosed/enrolled, $n$ = 42 with plasma samples) are shown in the gray line (ng/mL). PKa activity in DXS-stimulated plasma from a representation cohort of 26 participants with HAE-C1INH is shown in the black line. (**B**) HK and PK were quantified using a capillary-based immunoassay in DXS-stimulated whole plasma from a representative cohort of 6 individuals with HAE-C1INH. Bar graphs show percentage compared with plasma PK and HK levels in the absence of DXS stimulation (arithmetic mean ± SEM). DXS, dextran sulfate; HK, high-molecular-weight kininogen; PK, plasma prekallikrein; SD, standard deviation of the mean (modified from [44,54]). Figure panel A reprinted/adapted with permission from Ref. [44]. 2022 KalVista Pharmaceuticals, Inc. Figure panel B was published in *Lancet*, 401(10375), Aygören-Pürsün E, et al., An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial, pages 458-469, Copyright Elsevier 2023.

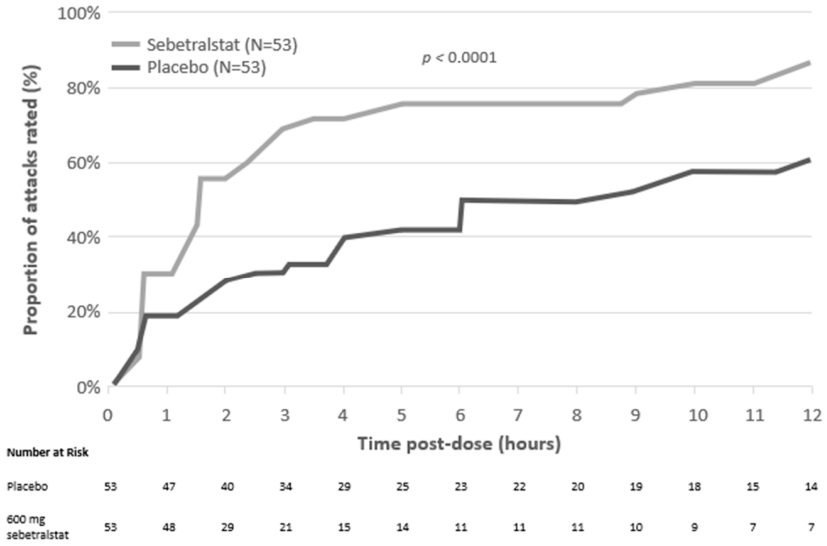



**Figure 7.** Time to symptom relief and proportion of attacks rated at least "a little better" on the Patient Global Impression of Change (PGI-C) for two consecutive timepoints within 12 h of study drug administration. Number at risk is the count of individuals who have not yet experienced the event and have not been censored (modified from [54]). This figure was published in *Lancet*, 401(10375), Aygören-Pürsün E, et al., An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial, pages 458–469, Copyright Elsevier 2023.

Following oral sebetralstat, the time for the near-complete inhibition of PKa activity and HK cleavage was as early as 15 min in part 1 and the time to the onset of symptom relief occurred at a median of 1.6 h in part 2. Since the half-life of circulating bradykinin is very short, blocking HK cleavage and the generation of bradykinin by PKa inhibition would be expected to rapidly halt the actions of the KKS. The strong inhibition of PKa activity with sebetralstat was shown to occur within minutes after dosing in both phase 1 and phase 2 studies. These results suggest that strong PKa inhibition mediates the symptom relief observed with sebetralstat. This is consistent with a mechanism of action where inhibition of HK cleavage would halt bradykinin generation and thereby rapidly block its effects and enable the restoration of endothelial barrier function. Moreover, the sebetralstat-mediated inhibition of the KKS feedback loop is expected to inhibit a further generation of both PKa and FXIIa (Figure 8). KONFIDENT (NCT05259917), a phase 3 study with sebetralstat for the on-demand treatment of HAE, was recently completed and is pending data readout [55].

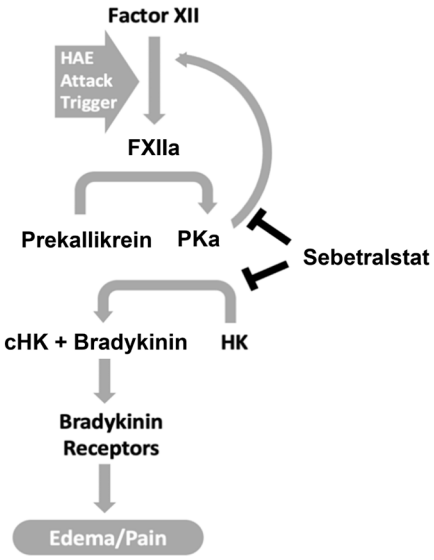



**Figure 8.** Schema of the effects of sebetralstat on the kallikrein kinin system (KKS). Sebetralstat inhibits plasma kallikrein (PKa)-mediated cleavage of high-molecular-weight kininogen (HK) that generates bradykinin and cleaved HK (cHK). Sebetralstat also inhibits the activation of Factor XII and the generation of PKa by the positive feedback amplification of the KKS. HAE, hereditary angioedema.

## 6. Summary and Conclusions

Sebetralstat is a competitive and reversible oral PKa inhibitor that rapidly blocks the actions of PKa, including the cleavage of HK that generates bradykinin and the feedback amplification of the KKS that increases the production of PKa. Structural studies show that sebetralstat induces a conformation change in the PKa active site, which contributes to its high potency for PKa and high selectivity against related serine proteases. The physiochemical properties of sebetralstat contribute to its rapid dissolution and efficient absorption, leading to its early $T_{max}$ and high exposure. A single dose of 600 mg of sebetralstat provided near-complete inhibition of PKa in as little as 15 min and was sustained for at least 4 h (the last timepoint measured) in patients with HAE. Dose–response studies in phase 1 showed that the duration of >90% PKa activity inhibition was maintained for 4 h and 6 h with a single dose of 300 mg and 600 mg of sebetralstat, respectively. The rapid inhibition of PKa after the oral administration of sebetralstat likely explains its rapid onset of symptom relief (median: 1.6 h) in a phase 2 trial for the on-demand treatment of HAE. Sebetralstat may provide a noninvasive on-demand treatment option to rapidly halt HAE attacks and provide fast symptom relief. The ease of use and portability with oral sebetralstat tablets could facilitate the early treatment of all attacks to control HAE.

**Funding:** This review article was funded by KalVista Pharmaceuticals.

**Institutional Review Board Statement:** This review article does not report primary research involving humans or animals. The protocols for the cited studies were approved by ethics review boards, as indicated in the primary publications.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data that support the findings of this review article are available from the corresponding author upon reasonable request.

**Conflicts of Interest:** All authors are employees of and own stock in KalVista Pharmaceuticals.

## References

1. Longhurst, H.; Cicardi, M. Hereditary Angio-Oedema. *Lancet* **2012**, *379*, 474–481. [CrossRef] [PubMed]
2. Bork, K.; Meng, G.; Staubach, P.; Hardt, J. Hereditary Angioedema: New Findings Concerning Symptoms, Affected Organs, and Course. *Am. J. Med.* **2006**, *119*, 267–274. [CrossRef] [PubMed]
3. Bork, K.; Hardt, J.; Schicketanz, K.-H.; Ressel, N. Clinical Studies of Sudden Upper Airway Obstruction in Patients with Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency. *Arch. Intern. Med.* **2003**, *163*, 1229–1235. [CrossRef] [PubMed]
4. Maat, S.D.; Hofman, Z.L.M.; Maas, C. Hereditary Angioedema: The Plasma Contact System Out of Control. *J. Thromb. Haemost.* **2018**, *16*, 1674–1685. [CrossRef] [PubMed]
5. Busse, P.; Kaplan, A. Specific Targeting of Plasma Kallikrein for Treatment of Hereditary Angioedema: A Revolutionary Decade. *J. Allergy Clin. Immunol. Pract.* **2021**, *10*, 716–722. [CrossRef] [PubMed]
6. Busse, P.J.; Christiansen, S.C. Hereditary Angioedema. *New Engl. J. Med.* **2020**, *382*, 1136–1148. [CrossRef] [PubMed]
7. Hofman, Z.L.M.; de Maat, S.; Suffritti, C.; Zanichelli, A.; van Doorn, C.; Sebastian, S.A.E.; Veszeli, N.; Csuka, D.; Renné, T.; Pasterkamp, G.; et al. Cleaved Kininogen as a Biomarker for Bradykinin Release in Hereditary Angioedema. *J. Allergy Clin. Immun.* **2017**, *140*, 1700–1703.e8. [CrossRef] [PubMed]
8. Marceau, F.; Regoli, D. Bradykinin Receptor Ligands: Therapeutic Perspectives. *Nat. Rev. Drug Discov.* **2004**, *3*, 845–852. [CrossRef] [PubMed]
9. Shen, J.; Zhang, H. Function and Structure of Bradykinin Receptor 2 for Drug Discovery. *Acta Pharmacol. Sin.* **2023**, *44*, 489–498. [CrossRef] [PubMed]
10. Marceau, F.; Bachelard, H.; Bouthillier, J.; Fortin, J.-P.; Morissette, G.; Bawolak, M.-T.; Charest-Morin, X.; Gera, L. Bradykinin Receptors: Agonists, Antagonists, Expression, Signaling, and Adaptation to Sustained Stimulation. *Int. Immunopharmacol.* **2020**, *82*, 106305. [CrossRef] [PubMed]
11. Davis, A.E.; Mejia, P.; Lu, F. Biological Activities of C1 Inhibitor. *Mol. Immunol.* **2008**, *45*, 4057–4063. [CrossRef]
12. Christiansen, S.C.; Wilmot, J.; Castaldo, A.J.; Zuraw, B.L. The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities. *Ann. Allergy Asthma Immunol.* **2023**, *131*, 766–774. [CrossRef] [PubMed]
13. Bouillet, L.; Bocquet, A.; Belbezier, A.; Boccon-Gibod, I. Effectiveness of Lanadelumab in Patients with Hereditary Angioedema with Normal C1 Inhibitor and FXII Mutation. *Ann. Allergy Asthma Immunol.* **2021**, *127*, 391–392. [CrossRef] [PubMed]
14. Santacroce, R.; D'Andrea, G.; Maffione, A.B.; Margaglione, M.; d'Apolito, M. The Genetics of Hereditary Angioedema: A Review. *J. Clin. Medicine* **2021**, *10*, 2023. [CrossRef] [PubMed]
15. Adatia, A.; Ritchie, B. Successful Use of Lanadelumab in a Patient with Hereditary Angioedema with Normal C1 Inhibitor and Negative Genetic Testing. *J. Allergy Clin. Immunol. Glob.* **2023**, *2*, 100087. [CrossRef] [PubMed]
16. Riedl, M.A.; Danese, M.; Danese, S.; Ulloa, J.; Maetzel, A.; Audhya, P.K. Hereditary Angioedema with Normal C1 Inhibitor: US Survey of Prevalence and Provider Practice Patterns. *J. Allergy Clin. Immunol. Pract.* **2023**, *11*, 2450–2456.e6. [CrossRef] [PubMed]
17. Bernstein, J.A.; Qazi, M. Ecallantide: Its Pharmacology, Pharmacokinetics, Clinical Efficacy and Tolerability. *Expert. Rev. Clin. Immunol.* **2010**, *6*, 29–39. [CrossRef] [PubMed]
18. US Food and Drug Administration. FDA Labelling Information—Kalbitor (Ecallantide). Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125277s081lbl.pdf (accessed on 3 April 2024).
19. Levy, R.J.; Lumry, W.R.; McNeil, D.L.; Li, H.H.; Campion, M.; Horn, P.T.; Pullman, W.E. EDEMA4: A Phase 3, Double-Blind Study of Subcutaneous Ecallantide Treatment for Acute Attacks of Hereditary Angioedema. *Ann. Allergy Asthma Immunol.* **2010**, *104*, 523–529. [CrossRef] [PubMed]
20. Craig, T.J.; Li, H.H.; Riedl, M.; Bernstein, J.A.; Lumry, W.R.; MacGinnitie, A.J.; Stolz, L.E.; Biedenkapp, J.; Chyung, Y. Characterization of Anaphylaxis After Ecallantide Treatment of Hereditary Angioedema Attacks. *J. Allergy Clin. Immunol. Pract.* **2015**, *3*, 206–212.e4. [CrossRef] [PubMed]
21. Duffey, H.; Firszt, R. Management of Acute Attacks of Hereditary Angioedema: Role of Ecallantide. *J. Blood Med.* **2015**, *6*, 115–123. [CrossRef] [PubMed]
22. Maurer, M.; Magerl, M.; Betschel, S.; Aberer, W.; Ansotegui, I.J.; Aygören-Pürsün, E.; Banerji, A.; Bara, N.-A.; Boccon-Gibod, I.; Bork, K.; et al. The International WAO/EAACI Guideline for the Management of Hereditary Angioedema—The 2021 Revision and Update. *World Allergy Organ. J.* **2022**, *15*, 100627. [CrossRef] [PubMed]

23. US Food and Drug Administration. FDA Labelling Information—FIRAZYR (Icatibant). Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022150s000lbl.pdf (accessed on 3 April 2024).
24. Lumry, W.R.; Li, H.H.; Levy, R.J.; Potter, P.C.; Farkas, H.; Moldovan, D.; Riedl, M.; Li, H.; Craig, T.; Bloom, B.J.; et al. Randomized Placebo-Controlled Trial of the Bradykinin B2 Receptor Antagonist Icatibant for the Treatment of Acute Attacks of Hereditary Angioedema: The FAST-3 Trial. *Ann. Allergy Asthma Immunol.* **2011**, *107*, 529–537.e2. [CrossRef] [PubMed]
25. Lumry, W.R.; Farkas, H.; Moldovan, D.; Toubi, E.; Baptista, J.; Craig, T.; Riedl, M. Icatibant for Multiple Hereditary Angioedema Attacks across the Controlled and Open-Label Extension Phases of FAST-3. *Int. Arch. Allergy Immunol.* **2015**, *168*, 44–55. [CrossRef] [PubMed]
26. Tachdjian, R.; Savic, S.; Fridman, M.; Frade, J.P.; Fasehun, M.; Audhya, P.K. Real-World Reporting Rates of Administration-Site Reactions with on-Demand Treatment of Hereditary Angioedema Attacks. *Allergy Asthma Proc.* **2024**, *45*, 37–43. [CrossRef] [PubMed]
27. Maurer, M.; Church, M.K. Inflammatory Skin Responses Induced by Icatibant Injection Are Mast Cell Mediated and Attenuated by H1-antihistamines. *Exp. Dermatol.* **2012**, *21*, 154–155. [CrossRef] [PubMed]
28. McNeil, B.D.; Pundir, P.; Meeker, S.; Han, L.; Undem, B.J.; Kulka, M.; Dong, X. Identification of a Mast-Cell-Specific Receptor Crucial for Pseudo-Allergic Drug Reactions. *Nature* **2015**, *519*, 237–241. [CrossRef] [PubMed]
29. Porebski, G.; Kwiecien, K.; Pawica, M.; Kwitniewski, M. Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions. *Front. Immunol.* **2018**, *9*, 3027. [CrossRef]
30. Alkanfari, I.; Gupta, K.; Jahan, T.; Ali, H. Naturally Occurring Missense MRGPRX2 Variants Display Loss of Function Phenotype for Mast Cell Degranulation in Response to Substance P, Hemokinin-1, Human β-Defensin-3, and Icatibant. *J. Immunol.* **2018**, *201*, 343–349. [CrossRef] [PubMed]
31. Yang, F.; Limjunyawong, N.; Peng, Q.; Schroeder, J.T.; Saini, S.; MacGlashan, D.; Dong, X.; Gao, L. Biological Screening of a Unique Drug Library Targeting MRGPRX2. *Front. Immunol.* **2022**, *13*, 997389. [CrossRef]
32. Kolkhir, P.; Ali, H.; Babina, M.; Ebo, D.; Sabato, V.; Elst, J.; Frischbutter, S.; Pyatilova, P.; Maurer, M. MRGPRX2 in Drug Allergy: What We Know and What We Do Not Know. *J. Allergy Clin. Immunol.* **2023**, *151*, 410–412. [CrossRef] [PubMed]
33. Banerji, A.; Riedl, M.A.; Bernstein, J.A.; Cicardi, M.; Longhurst, H.J.; Zuraw, B.L.; Busse, P.J.; Anderson, J.; Magerl, M.; Martinez-Saguer, I.; et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *Jama* **2018**, *320*, 2108. [CrossRef] [PubMed]
34. Zuraw, B.; Lumry, W.R.; Johnston, D.T.; Aygören-Pürsün, E.; Banerji, A.; Bernstein, J.A.; Christiansen, S.C.; Jacobs, J.S.; Sitz, K.V.; Gower, R.G.; et al. Oral Once-Daily Berotralstat for the Prevention of Hereditary Angioedema Attacks: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial. *J. Allergy Clin. Immun.* **2021**, *148*, 164–172.e9. [CrossRef] [PubMed]
35. Aberer, W.; Maurer, M.; Bouillet, L.; Zanichelli, A.; Caballero, T.; Longhurst, H.J.; Perrin, A.; Andresen, I.; Aberer, W.; Wiednig, M.; et al. Breakthrough Attacks in Patients with Hereditary Angioedema Receiving Long-Term Prophylaxis Are Responsive to Icatibant: Findings from the Icatibant Outcome Survey. *Allergy Asthma Clin. Immunol.* **2017**, *13*, 31. [CrossRef] [PubMed]
36. Yong, P.F.K.; Coulter, T.; El-Shanwany, T.; Garcez, T.; Hackett, S.; Jain, R.; Kiani-Alikhan, S.; Manson, A.; Noorani, S.; Stroud, C.; et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. *J. Allergy Clin. Immunol. Pract.* **2023**, *11*, 2476–2483. [CrossRef] [PubMed]
37. Mendivil, J.; DerSarkissian, M.; Banerji, A.; Diwakar, L.; Katelaris, C.H.; Keith, P.K.; Kim, H.; Lacuesta, G.; Magerl, M.; Slade, C.; et al. A Multicenter Chart Review of Patient Characteristics, Treatment, and Outcomes in Hereditary Angioedema: Unmet Need for More Effective Long-Term Prophylaxis. *Allergy Asthma Clin. Immunol.* **2023**, *19*, 48. [CrossRef] [PubMed]
38. Bouillet, L.; Fain, O.; Armengol, G.; Aubineau, M.; Blanchard-Delaunay, C.; Dalmas, M.-C.; Moreuil, C.D.; Thanh, A.D.; Gobert, D.; Guez, S.; et al. Long-Term Prophylaxis in Hereditary Angioedema Management: Current Practices in France and Unmet Needs. *Allergy Asthma Proc.* **2022**, *43*, 406–412. [CrossRef] [PubMed]
39. Busse, P.J.; Christiansen, S.C.; Riedl, M.A.; Banerji, A.; Bernstein, J.A.; Castaldo, A.J.; Craig, T.; Davis-Lorton, M.; Frank, M.M.; Li, H.H.; et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 132–150.e3. [CrossRef] [PubMed]
40. Craig, T.J.; Rojavin, M.A.; Machnig, T.; Keinecke, H.-O.; Bernstein, J.A. Effect of Time to Treatment on Response to C1 Esterase Inhibitor Concentrate for Hereditary Angioedema Attacks. *Ann. Allergy Asthma Immunol.* **2013**, *111*, 211–215. [CrossRef] [PubMed]
41. Maurer, M.; Aberer, W.; Bouillet, L.; Caballero, T.; Fabien, V.; Kanny, G.; Kaplan, A.; Longhurst, H.; Zanichelli, A. Hereditary Angioedema Attacks Resolve Faster and Are Shorter after Early Icatibant Treatment. *PLoS ONE* **2013**, *8*, 1–7. [CrossRef]
42. FDA The Voice of the Patient: Hereditary Angioedema. Silver Spring (Md): US Food and Drug Administration; Center for Biologics Evaluation and Research; 2018. Available online: https://www.fda.gov/files/about%20fda/published/The-Voice-of-the-Patient---Hereditary-Angioedema.pdf (accessed on 3 April 2024).
43. Maetzel, A.; Smith, M.D.; Duckworth, E.J.; Hampton, S.L.; Donatis, G.M.D.; Murugesan, N.; Rushbrooke, L.J.; Li, L.; Francombe, D.; Feener, E.P.; et al. KVD900, an Oral on-Demand Treatment for Hereditary Angioedema: Phase 1 Study Results. *J. Allergy Clin. Immun.* **2022**, *149*, 2034–2042. [CrossRef] [PubMed]
44. Duckworth, E.J.; Murugesan, N.; Li, L.; Rushbrooke, L.J.; Lee, D.K.; Donatis, G.M.D.; Maetzel, A.; Yea, C.M.; Hampton, S.L.; Feener, E.P. Pharmacological Suppression of the Kallikrein Kinin System with KVD900: An Orally Available Plasma Kallikrein Inhibitor for the On-demand Treatment of Hereditary Angioedema. *Clin. Exp. Allergy* **2022**, *52*, 1059–1070. [CrossRef] [PubMed]

45. Davie, R.L.; Edwards, H.J.; Evans, D.M.; Hodgson, S.T.; Stocks, M.J.; Smith, A.J.; Rushbrooke, L.J.; Pethen, S.J.; Roe, M.B.; Clark, D.E.; et al. Sebetralstat (KVD900): A Potent and Selective Small Molecule Plasma Kallikrein Inhibitor Featuring a Novel P1 Group as a Potential Oral On-Demand Treatment for Hereditary Angioedema. *J. Med. Chem.* **2022**, *65*, 13629–13644. [CrossRef] [PubMed]
46. Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K.-H.; Reinemer, P.; Perzborn, E. Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-Oxo-3-[4-(3-Oxomorpholin-4-Yl)Phenyl]-1,3-Oxazolidin-5-Yl}methyl)Thiophene- 2-Carboxamide (BAY 59-7939): An Oral, Direct Factor Xa Inhibitor. *J. Med. Chem.* **2005**, *48*, 5900–5908. [CrossRef] [PubMed]
47. Lam, P.Y.S.; Clark, C.G.; Li, R.; Pinto, D.J.P.; Orwat, M.J.; Galemmo, R.A.; Fevig, J.M.; Teleha, C.A.; Alexander, R.S.; Smallwood, A.M.; et al. Structure-Based Design of Novel Guanidine/Benzamidine Mimics: Potent and Orally Bioavailable Factor Xa Inhibitors as Novel Anticoagulants. *J. Med. Chem.* **2003**, *46*, 4405–4418. [CrossRef]
48. Li, Z.; Partridge, J.R.; Silva-Garcia, A.; Rademacher, P.; Betz, A.; Xu, Q.; Sham, H.L.; Hu, Y.; Shan, Y.; Liu, B.; et al. Structure-Guided Design of Novel, Potent and Selective Macrocyclic Plasma Kallikrein Inhibitors. *ACS Med. Chem. Lett.* **2016**, *8*, 185–190. [CrossRef] [PubMed]
49. Monteiro, A.C.; Schmitz, V.; Morrot, A.; de Arruda, L.B.; Nagajyothi, F.; Granato, A.; Pesquero, J.B.; Müller-Esterl, W.; Tanowitz, H.B.; Scharfstein, J. Bradykinin B2 Receptors of Dendritic Cells, Acting as Sensors of Kinins Proteolytically Released by Trypanosoma Cruzi, Are Critical for the Development of Protective Type-1 Responses. *PLoS Pathog.* **2007**, *3*, e185. [CrossRef] [PubMed]
50. Girolami, J.-P.; Bouby, N.; Richer-Giudicelli, C.; Alhenc-Gelas, F. Kinins and Kinin Receptors in Cardiovascular and Renal Diseases. *Pharmaceuticals* **2021**, *14*, 240. [CrossRef] [PubMed]
51. Petersen, R.S.; Bordone, L.; Riedl, M.A.; Tachdjian, R.; Craig, T.J.; Lumry, W.R.; Manning, M.E.; Bernstein, J.A.; Raasch, J.; Zuraw, B.L.; et al. A Phase 2 Open-label Extension Study of Prekallikrein Inhibition with Donidalorsen for Hereditary Angioedema. *Allergy* **2023**, *79*, 724–734. [CrossRef] [PubMed]
52. Ponczek, M.B.; Shamanaev, A.; LaPlace, A.; Dickeson, S.K.; Srivastava, P.; Sun, M.; Gruber, A.; Kastrup, C.; Emsley, J.; Gailani, D. The Evolution of Factor XI and the Kallikrein-Kinin System. *Blood Adv.* **2020**, *4*, 6135–6147. [CrossRef] [PubMed]
53. Mutch, P.; Bashir, M.; Jung, B.; Yi, P.; Iverson, M. Absorption, Metabolism, and Excretion of [14C]-Sebetralstat (KVD900) Following a Single Oral Dose in Healthy Male Participants. *Xenobiotica* **2022**, *52*, 707–717. [CrossRef]
54. Aygören-Pürsün, E.; Zanichelli, A.; Cohn, D.M.; Cancian, M.; Hakl, R.; Kinaciyan, T.; Magerl, M.; Martinez-Saguer, I.; Stobiecki, M.; Farkas, H.; et al. An Investigational Oral Plasma Kallikrein Inhibitor for On-Demand Treatment of Hereditary Angioedema: A Two-Part, Randomised, Double-Blind, Placebo-Controlled, Crossover Phase 2 Trial. *Lancet* **2023**, *401*, 458–469. [CrossRef] [PubMed]
55. Cohn, D.M.; Aygören-Pürsün, E.; Bernstein, J.A.; Farkas, H.; Lumry, W.R.; Maurer, M.; Zanichelli, A.; Iverson, M.; Hao, J.; Smith, M.D.; et al. Evaluation of Patient-reported Outcome Measures for On-demand Treatment of Hereditary Angioedema Attacks and Design of KONFIDENT, a Phase 3 Trial of Sebetralstat. *Clin. Transl. Allergy* **2023**, *13*, e12288. [CrossRef] [PubMed]


**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.