

ORAL SEBETRALSTAT FOR THE TREATMENT OF AN ATTACK OF HEREDITARY ANGIOEDEMA

The present invention relates to treatments of hereditary angioedema (HAE). In particular, the present invention provides on-demand treatments of hereditary angioedema (HAE) by orally administering a plasma kallikrein inhibitor to a patient in need thereof on-demand.

Background to the invention

Inhibitors of plasma kallikrein have a number of therapeutic applications, particularly in the treatment of hereditary angioedema.

Plasma kallikrein (PKa) is a trypsin-like serine protease that can liberate kinins from kininogens (see K. D. Bhoola *et al.*, "Kallikrein-Kinin Cascade", *Encyclopedia of Respiratory Medicine*, p483-493; J. W. Bryant *et al.*, "Human plasma kallikrein-kinin system: physiological and biochemical parameters" *Cardiovascular and haematological agents in medicinal chemistry*, 7, p234-250, 2009; K. D. Bhoola *et al.*, *Pharmacological Rev.*, 1992, **44**, 1; and D. J. Campbell, "Towards understanding the kallikrein-kinin system: insights from the measurement of kinin peptides", *Brazilian Journal of Medical and Biological Research* 2000, **33**, 665-677). Plasma prekallikrein is encoded by a single gene and is mainly synthesized in the liver, as well as other tissues. It is secreted by hepatocytes as a zymogen that circulates in plasma as a heterodimer complex bound to high molecular weight kininogen (HK) which is activated to give the active PKa. Factor XIIa (FXIIa) mediates conversion of plasma prekallikrein to PKa, which is a serine protease that cleaves high molecular weight kininogen (HK) to generate bradykinin, a potent inflammatory hormone. Kinins are potent mediators of inflammation that act through G protein-coupled receptors and antagonists of kinins (such as bradykinin receptor antagonists) have previously been investigated as potential therapeutic agents for the treatment of a number of disorders (F. Marceau and D. Regoli, *Nature Rev., Drug Discovery*, 2004, **3**, 845-852).

Activation of the kallikrein-kinin system (KKS) is initiated by a variety of physiological (e.g. negatively charged surfaces) and pathological factors, which induce a conformational change in FXII leading to its cleavage and activation by certain proteases e.g. plasmin (Hofman *et al* *Clin Rev Allergy Immunol* 2016), which may not require negative surfaces, or by misfolded proteins (Maas *et al* *J Clinical Invest* 2008). Activation of plasma prekallikrein to PKa by FXIIa is followed by reciprocal activation of FXII to FXIIa by PKa and thereby provides positive feedback amplification of the KKS.

The biologically active peptide bradykinin activates bradykinin 2 receptors (B2R) that are expressed on a variety of vascular, neuronal, and immune cell types (Kaplan AP, Joseph K. Pathogenic mechanisms of bradykinin mediated diseases: dysregulation of an innate inflammatory pathway. *Adv Immunol.* 2014;121:41-89). The interaction between bradykinin and B2R activates proinflammatory signalling pathways that mediate, for example, angioedema, pain, inflammation, chemotaxis of neutrophils, vascular hyperpermeability, and vasodilatation (see Kaplan et al., *Adv Immunol.* 2014;121:41-89; and Hopp et al., *J Neuroinflammation.* 2017 Feb 20;14(1):39).

PKa is thought to play a role in a number of inflammatory disorders. The major inhibitor of PKa is the serpin C1 esterase inhibitor (C1INH). People with a genetic deficiency in C1INH levels or function due to mutation in *SERPING1* can develop hereditary angioedema (HAE-C1INH) which can result in intermittent swelling of face, extremities, larynx, gastro-intestinal tract and genitals. Plasma from HAE patients have increased levels of cleaved HK, which indicates the generation of bradykinin (PLoS ONE 8(8): e74043. 2013). Treatment with PKa inhibitors, (such as the approved medicinal products ecallantide, lanadelumab, and berotralstat) has been shown to effectively treat HAE- C1INH.

Hereditary angioedema (HAE) is a rare inherited disorder characterised by recurrent acute attacks where fluids accumulate outside of the blood vessels, blocking the normal flow of blood or lymphatic fluid and causing rapid swelling of tissues such as in the hands, feet, limbs, face, intestinal tract, or airway. "Hereditary angioedema" can thus be defined as any disorder characterised by recurrent episodes of bradykinin-mediated angioedema (e.g. severe swelling) caused by an inherited dysfunction/fault/mutation. There are currently three known categories of HAE: (i) HAE type 1, (ii) HAE type 2, and (iii) HAE with normal C1INH levels and function (HAE-nC1INH). However, the HAE field is developing quickly so it is expected that further types of HAE might be defined in the future.

Without wishing to be bound by theory, it is thought that HAE type 1 is caused by mutations in the *SERPING1* gene that lead to reduced levels of C1INH in the blood. Without wishing to be bound by theory, it is thought that HAE type 2 is caused by mutations in the *SERPING1* gene that lead to dysfunction of the C1INH in the blood.

Unlike HAE types 1 and 2 (also called HAE-C1INH), the pathophysiology of HAE-nC1INH is heterogeneous and not fully understood. Without wishing to be bound by theory, the cause of HAE-nC1INH is less well-defined and the underlying genetic dysfunction/fault/mutation can sometimes remain unknown. What is known is that the cause of HAE-nC1INH is not related to reduced levels or dysfunction of the C1INH (in contrast to HAE types 1 and 2).

Currently, there are difficulties in diagnosing patients with HAE-nC1INH. Indeed, the absence of universally accepted criteria for the diagnosis of HAE-nC1INH limits estimates of its prevalence. At present, HAE-nC1INH can be diagnosed by reviewing the family history and noting that angioedema has been inherited from a previous generation (and thus it is hereditary angioedema). HAE-nC1INH can also be diagnosed by determining that there is a dysfunction/fault/mutation in a gene other than those related to C1INH. For example, it has been reported that dysfunction/fault/mutation with plasminogen can cause HAE-nC1INH (see e.g. Veronez et al., *Front Med (Lausanne)*. 2019 Feb 21;6:28; or Recke et al., *Clin Transl Allergy*. 2019 Feb 14;9:9.). It has also been reported that dysfunction/fault/mutation with *F12* gene and Factor XII can cause HAE-nC1INH (see e.g. Mansi et al., 2014 *The Association for the Publication of the Journal of Internal Medicine Journal of Internal Medicine*, 2015, 277; 585–593; or Maat et al. *J Thromb Haemost*. 2019 Jan;17(1):183-194). However, the genetic cause in most patients with HAE-nC1INH is unknown, and this subtype is referred as HAE-UNK or AE-UNK (Bork K et al. *Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations*. *Allergy*. 2015 Aug;70(8):1004-12, Bork K et al. *Gene Mutations Linked to Hereditary Angioedema in Solitary Angioedema Patients With Normal C1 Inhibitor*. *J Allergy Clin Immunol Pract*. 2023 Aug;11(8):2441-2449). About 87% of patients diagnosed with HAE-nC1INH have an unknown mutation, limiting the utility of genetic tests to establish the diagnosis.

Acute HAE attacks (shortened to “HAE attacks”) normally progress through three key clinically distinct stages: an initial prodromal stage (that can typically last for up to 12 hours), followed by a swelling stage, and then an absorption stage. A majority of HAE attacks announce themselves with prodromal symptoms. Two thirds of prodromes appeared less than 6 hours before a HAE attack and no prodromes occur more than 24 hours before a HAE attack (Magerl *et al.*, *Clinical and Experimental Dermatology* 2014, **39**, 298-303). For example, the following prodromal symptoms may start to be observed: a slight swelling (particularly affecting the face and neck), a typical type of abdominal pain, a typical reddening of the skin called “erythema marginatum”. An attack is fully developed when it has reached maximum swelling and maximum expression of pain (e.g. abdominal attack), discomfort (e.g. peripheral attack) or threat to life (e.g. laryngeal attack). Once the attack has reached its peak, the subsequent time period to normalization is determined by the time it takes for the swelling to disappear and the liquid that has penetrated the tissues to be reabsorbed.

Synthetic and small molecule plasma kallikrein inhibitors have been described previously, for example by Garrett *et al.* (“Peptide aldehyde....” *J. Peptide Res.* **52**, 62-71 (1998)), T. Griesbacher *et al.* (“Involvement of tissue kallikrein but not plasma kallikrein in the development of symptoms mediated by endogenous kinins in acute pancreatitis in rats” *British Journal of Pharmacology* **137**, 692-700 (2002)), Evans (“Selective

dipeptide inhibitors of kallikrein" WO03/076458), Szelke *et al.* ("Kininogenase inhibitors" WO92/04371), D. M. Evans *et al.* (*Immunopharmacology*, 32, p115-116 (1996)), Szelke *et al.* ("Kininogen inhibitors" WO95/07921), Antonsson *et al.* ("New peptides derivatives" WO94/29335), J. Corte *et al.* ("Six membered heterocycles useful as serine protease inhibitors" WO2005/123680), J. Stürzbecher *et al.* (Brazilian J. Med. Biol. Res 27, p1929-34 (1994)), Kettner *et al.* (US 5,187,157), N. Teno *et al.* (Chem. Pharm. Bull. 41, p1079-1090 (1993)), W. B. Young *et al.* ("Small molecule inhibitors of plasma kallikrein" Bioorg. Med. Chem. Letts. 16, p2034-2036 (2006)), Okada *et al.* ("Development of potent and selective plasmin and plasma kallikrein inhibitors and studies on the structure-activity relationship" Chem. Pharm. Bull. 48, p1964-72 (2000)), Steinmetzer *et al.* ("Trypsin-like serine protease inhibitors and their preparation and use" WO08/049595), Zhang *et al.* ("Discovery of highly potent small molecule kallikrein inhibitors" Medicinal Chemistry 2, p545-553 (2006)), Sinha *et al.* ("Inhibitors of plasma kallikrein" WO08/016883), Shigenaga *et al.* ("Plasma Kallikrein Inhibitors" WO2011/118672), and Kolte *et al.* ("Biochemical characterization of a novel high-affinity and specific kallikrein inhibitor", *British Journal of Pharmacology* (2011), **162**(7), 1639-1649). Also, Steinmetzer *et al.* ("Serine protease inhibitors" WO2012/004678) describes cyclized peptide analogs which are inhibitors of human plasmin and plasma kallikrein.

As explained above, HAE can manifest in patients who present with a genetic deficiency or dysfunction in C1 esterase inhibitor. Thus, some of the current treatments of HAE involve administering a C1 esterase inhibitor to normalise the deficiency or dysfunction in C1 esterase inhibitor. Such treatments can be prophylactic (*i.e.* administered in the absence of acute HAE attack symptoms to prevent/reduce the likelihood of an acute HAE attack) and/or acute treatments (*i.e.* administered when acute HAE attack symptoms are noticed to try to stop or reduce the severity of the acute HAE attack).

Cinryze® and Haegarda® contain a C1 esterase inhibitor and are authorised to prevent acute HAE attacks (*i.e.* prophylactic treatment). Treatment with Cinryze® requires the preparation of a solution from a powder, which is then injected every 3 or 4 days. Similarly, treatment with Haegarda® requires the preparation of a solution from a powder, which is then injected twice a week. It is not always possible for a patient to self-administer these treatments, and if this is the case, the patient is required to visit a clinic for treatment. Thus, both of these prophylactic treatments suffer from high patient burden. Additionally, the FDA packet insert for Haegarda® states that it "should not be used to treat an acute HAE attack", and therefore a patient may require additional therapy if a HAE attack develops.

Berinert® and Ruconest® contain a C1 esterase inhibitor and are authorised to treat acute HAE attacks. Both of these treatments also involve the preparation of an injectable solution followed by injection. This process can be burdensome on the patient, especially when the patient is suffering from an acute HAE

attack. Self-administration of the dosage amount is also not always possible, and if it is not, administration of the drug can be substantially delayed thus increasing the severity of the acute HAE attack for the patient.

5 Kalbitor® (active substance ecallantide) and Takhzyro® (active substance lanadelumab) are selective plasma kallikrein inhibitors approved for medical use in the treatment of HAE. Both treatments are formulated as solutions for injection. Ecallantide is a large protein plasma kallikrein inhibitor that presents a risk of anaphylactic reactions. Indeed, the EU marketing authorisation application for Kalbitor® has recently been withdrawn because the benefits of Kalbitor® are said to not outweigh its risks. Lanadelumab
10 is a recombinant fully human IgG1 kappa light chain monoclonal antibody. Reported adverse reactions of treatment with lanadelumab include hypersensitivity, injection site pain, injection site erythema, and injection site bruising. The authorised EMA label for Takhzyro® (active substance lanadelumab) states that it “is not intended for treatment of acute HAE attacks” and that “in case of a breakthrough HAE attack, individualized treatment should be initiated with an approved rescue medication”. Also, as injections,
15 both of these treatments involve a high patient burden.

Berotrastat (BCX7353) has been approved in some countries for preventative treatment of HAE (not as an on-demand treatment), e.g. under the brand name Orladeyo®. Hwang et al. (Immunotherapy (2019) 11(17), 1439–1444) states that higher doses were associated with more gastrointestinal adverse effects
20 indicating increased toxicity at higher levels.

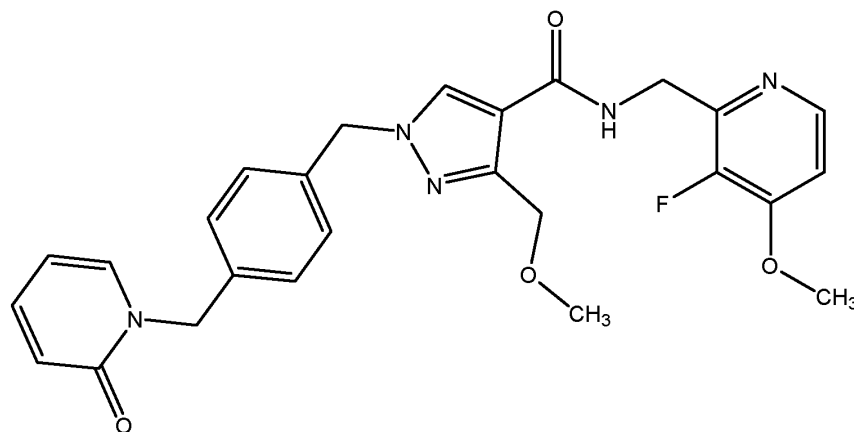
Furthermore, many molecules in the known art feature a highly polar and ionisable guanidine or amidine functionality. It is well known that such functionalities may be limiting to gut permeability and therefore to oral availability. For example, it has been reported by Tamie J. Chilcote and Sukanto Sinha (“ASP-634:
25 An Oral Drug Candidate for Diabetic MacularEdema”, ARVO 2012 May 6th – May 9th, 2012, Fort Lauderdale, Florida, Presentation 2240) that ASP-440, a benzamidine, suffers from poor oral availability. It is further reported that absorption may be improved by creating a prodrug such as ASP-634. However, it is well known that prodrugs can suffer from several drawbacks, for example, poor chemical stability and potential toxicity from the inert carrier or from unexpected metabolites. In another report, indole amides
30 are claimed as compounds that might overcome problems associated with drugs possessing poor or inadequate ADME-tox and physicochemical properties although no inhibition against plasma kallikrein is presented or claimed (Griffioen *et al.*, “Indole amide derivatives and related compounds for use in the treatment of neurodegenerative diseases”, WO2010142801).

Other plasma kallikrein inhibitors known in the art are generally small molecules, some of which include highly polar and ionisable functional groups, such as guanidines or amidines. Recently, plasma kallikrein inhibitors that do not feature guanidine or amidine functionalities have been reported. For example Brandl *et al.* ("N-((6-amino-pyridin-3-yl)methyl)-heteroaryl-carboxamides as inhibitors of plasma kallikrein" WO2012/017020), Evans *et al.* ("Benzylamine derivatives as inhibitors of plasma kallikrein" 5 WO2013/005045), Allan *et al.* ("Benzylamine derivatives" WO2014/108679), Davie *et al.* ("Heterocyclic derivatives" WO2014/188211), Davie *et al.* ("N-((het)arylmethyl)-heteroaryl-carboxamides compounds as plasma kallikrein inhibitors" WO2016/083820).

10 The applicant has developed a novel series of compounds that are inhibitors of plasma kallikrein, which are disclosed in WO2016/083820 (PCT/GB2015/053615). These compounds demonstrate good selectivity for plasma kallikrein. One such compound is N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide.

15 The name N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide denotes the structure depicted below, which is known by its codename "KVD900". The INN for KVD900 is sebetralstat, which is how this compound will be described throughout this application.

20



Sebetralstat.

Certain dosage forms comprising sebetralstat are disclosed in Collett *et al.* WO2019/106361. 25 Orodispersible tablets comprising sebetralstat are disclosed in WO2023/209381. Treatments of HAE comprising sebetralstat are discussed in WO2020/249977 and WO2022/084693.

Sebetralstat met all of its phase 2 efficacy and safety endpoints (see clinical trial NCT04208412). The results of this phase 2 study are discussed in WO2022/172006.

- 5 To date, there is a lack of approved oral treatments for HAE (see e.g. Craig et al. *Int Arch Allergy Immunol.* 2014;165(2):119-27. doi: 10.1159/000368404; Mager et al., *Immunol Allergy Clin North Am.* 2017 Aug;37(3):571-584). There are no approved oral on-demand treatments for HAE. Instead, the majority of available treatments are injectables. Injectables suffer from many disadvantages compared to oral
- 10 oral treatments e.g. needing to be in a suitable environment to formulate and then administer the injection, and also causing pain at the injection site. Reduced patient compliance can lead to patients delaying treatment, which generally leads to attack symptoms getting worse, or even avoiding treatment altogether. Indeed, many patients suffering from HAE simply hope that any attack will dissipate on its own to avoid administering an injection. Injectable treatments suffer from late dosing because the patient may
- 15 need to prepare the dosage form or even travel to hospital for treatment. Therefore, HAE treatment is often undermined by late dosing caused by the high burden on the patient. Indeed, Maurer M et al. (*PLoS ONE* 2013;8(2): e53773. doi:10.1371/journal.pone.0053773) explains that more than 60% of patients administer their HAE injectable more than one hour after the onset of an attack.
- 20 Icatibant (marketed as Firazyr®) is the predominant on-demand treatment for HAE, and is administered by subcutaneous injection. In a real-world study of HAE patients with access to icatibant (Maurer M et al. *PLoS ONE* 2013;8(2): e53773. doi:10.1371/journal.pone.0053773), less than 40% of treated attacks were dosed within an hour of onset, with 30% not being treated until over 5 hours after onset. Further, 45% of attacks in this study were not treated at all. Therefore, there is an unmet need to provide patients with
- 25 improved treatment options to treat HAE attacks on-demand.

- HAE attacks resolve faster and are shorter after early treatment (Maurer M et al. *PLoS ONE* 2013;8(2): e53773. doi:10.1371/journal.pone.0053773) and thus early intervention when an attack is expected, or ongoing, is essential to desirably manage the disease. Nevertheless, there is currently a reliance on
- 30 injectable therapies for on-demand treatment of HAE patients, and further patient confidence that oral on-demand therapies can replace injectable therapies would be desirable. Patients must have confidence in any alternative (non-injectable) therapy if they are to move away from their current therapy to such alternative therapies.

Definitions

The terms "attack of HAE", "HAE attack", and "attack", etc. are used interchangeably herein. The term "hereditary angioedema" (shortened to HAE) means any bradykinin-mediated angioedema caused by an inherited genetic dysfunction, fault, or mutation. As a result, the term "HAE" includes at least HAE type 1, HAE type 2, and HAE with normal C1INH levels and function (HAE-nC1INH).

Sebetralstat used in the present invention can also be in the preferred crystalline form (Form 1), which exhibits at least the following characteristic X-ray powder diffraction peaks (Cu K α radiation, expressed in degrees 2 θ) at approximately:

- (1) 11.2, 12.5, 13.2, 14.5 and 16.3; or
- (2) 11.2, 12.5, 13.2, 14.5, 16.3, 17.4 and 17.9; or
- (3) 11.2, 12.5, 13.2, 14.5, 16.3, 17.4, 17.9, 21.2 and 22.0.

The term "approximately" means in this context that there is an uncertainty in the measurements of the degrees 2 θ of ± 0.3 (expressed in degrees 2 θ), preferably ± 0.2 (expressed in degrees 2 θ).

Form 1 can also have an X ray powder diffraction pattern comprising characteristic peaks (expressed in degrees 2 θ) at approximately 4.4, 11.2, 12.5, 13.2, 14.5, 16.3, 17.4, 17.9, 21.2, 22.0 and 22.6.

Form 1 can also have an X-ray powder diffraction pattern substantially the same as that shown in Figure 1.

In any of the treatments of the invention described herein, the term "sebetralstat" is shorthand for "sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)". It will be understood that "pharmaceutically acceptable salts and/or solvates thereof" means "pharmaceutically acceptable salts thereof", "pharmaceutically acceptable solvates thereof", and "pharmaceutically acceptable solvates of salts thereof". The preferred form of sebetralstat is the free base form, specifically the anhydrous free base form (when it is possible to keep the free base anhydrous).

The term "pharmaceutically acceptable salt" means a physiologically or toxicologically tolerable salt, which can be, for example, pharmaceutically acceptable acid addition salts. For instance, as sebetralstat contains a basic group, e.g. a basic nitrogen, pharmaceutically acceptable acid addition salts that can be formed include hydrochlorides, hydrobromides, sulfates, phosphates, acetates, citrates, lactates, tartrates, mesylates, succinates, oxalates, phosphates, esylates, tosylates, benzenesulfonates,

naphthalenedisulphonates, maleates, adipates, fumarates, hippurates, camphorates, xinafoates, acetamidobenzoates, dihydroxybenzoates, hydroxynaphthoates, succinates, ascorbates, oleates, bisulfates and the like. The preferred pharmaceutically acceptable salt of the compound is the hydrochloride salt.

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Hemisalts of acids can also be formed, for example, hemisulfate salts.

For a review of suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

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The term "solvate" is used herein to describe a molecular complex comprising sebetralstat and a one or more pharmaceutically acceptable solvent molecules, for example, ethanol or water. The term "hydrate" is employed when the solvent is water and for the avoidance of any doubt, the term "hydrate" is encompassed by the term "solvate".

15

"Sebetralstat" may include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds wherein hydrogen is replaced by deuterium or tritium, or wherein carbon is replaced by ^{13}C or ^{14}C , are within the scope of the present invention.

20 "On-demand" treatment, in the context of HAE, means that sebetralstat is administered upon need of therapy in connection with one specific HAE attack. "On-demand" does not require the administration of sebetralstat continuously at regular intervals (e.g. once a week, twice a week, etc.) irrespective of an instance of an HAE attack. This is in contrast to some other known treatments of HAE (e.g. treatments with Cinryze® and Haegarda®, as described above) that require continuous and regular dosing for therapy.

25 Instead, in treatments of the invention, sebetralstat is taken when the patient requires fast-acting therapeutic effects. These are discussed below in more detail.

In any of the treatments of the invention described herein, the patient is preferably a human. HAE can affect patients of all ages. Accordingly, the human patient can be a child (ages 0 to less than 18 years) or

30 an adult (18 years old or older). In any of the treatments described herein, the patient can have a predisposition to angioedema. Specifically, the patient can be aged 12 years and above. The patient can also be aged 2 years and above.

The human patient can be aged between 2 and less than 18. The human patient can be aged between 2 and less than 12. The human patient can be aged between 12 and less than 18. The patient can be at least 70 years old.

- 5 As used herein, the “second treatment of the HAE attack” or “second treatment” is the administration of any dose of active pharmaceutical ingredient for treating an HAE attack on-demand that is not sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The second treatment can be an existing HAE treatment. For example, the “second treatment” can be pdC1INH, rhC1INH, icatibant, conestat alfa (Ruconest®), or ecallantide. For the avoidance of any doubt, “second treatment of an HAE attack” does
10 not include prophylactic treatments of HAE.

As used herein, the terms “second dose”, “third dose”, “fourth dose” and “further dose” refer to the administration of a dose of sebetralstat subsequent to the initial dose.

- 15 “To resolve the attack” or “attack resolution”, unless specified otherwise, means that the HAE attack clears without the need for a further dose of sebetralstat or a second treatment.

- The term “consecutive time points” when used in the context of “symptom relief” can mean an assessment separated by 30 mins (particularly within 0-4 hours after administration of the compound).
20 “Consecutive time points” can also mean an assessment separated by 1 hour (particularly within 4-12 hours after administration of the compound). “Consecutive time points” can also mean an assessment separated by 3 hours (particularly within 12-24 hours after administration of the compound).

- As used herein, the term “orodispersible tablet” (ODT) means a tablet that is intended to be placed
25 directly in the mouth where they rapidly disintegrate in saliva before they are swallowed. An ODT is not a swallowable tablet, for instance a conventional swallowable tablet or capsule.

Description of the invention

- 30 The efficacy data from the phase 3 study described in Example 4 confirm that treatment with sebetralstat reduces the time to beginning of symptom relief, reduces the time to a reduction in attack severity and achieves complete attack resolution. These results are statistically significant.

More specifically, the efficacy data from the phase 3 study described in Example 4 report that sebetralstat treatment can be used across a wide range of attack locations and severities, including severe and very severe attacks, and including attacks of the neck and above, which can be life-threatening types of attack.

5 Further, the data described herein report that sebetralstat (a plasma kallikrein inhibitor) is effective in patients who are also being treated with a prophylactic HAE treatment (even when the prophylactic treatment is also a plasma kallikrein inhibitor). More specifically, the data described herein show that sebetralstat (a plasma kallikrein inhibitor) can be used on-demand to treat HAE attacks in patients who are also being treated with a prophylactic HAE treatment (even when the prophylactic treatment is also a plasma kallikrein inhibitor), even if the HAE attack is a severe or very severe attack and/or where the HAE attack is an attack of the neck and above but is not a laryngeal attack. The attack of the neck and above can be a facial attack (i.e., an attack of the face) and/or an attack of the tongue and/or an attack of the throat.

15 The phase 3 results report that sebetralstat provided rapid symptom relief in a broad HAE population that reflects clinical practice, and was safe and well-tolerated with a safety profile comparable with placebo. These results can provide patients with further confidence that they are able to treat a wide range of HAE attacks, including the most extreme attacks.

20 ***Treatment of severe or worse HAE attacks***

As noted above, HAE is a rare and potentially life-threatening genetic condition that involves recurrent attacks of unpredictable and often debilitating swelling in various parts of the body, including the hands, feet, genitals, stomach, face and/or throat. Severe attacks can be life-threatening and therefore it is of paramount importance that any on-demand treatment is fast-acting and effective.

Further, current on-demand treatments involve high patient burden such that patients do not treat early enough and often delay treatment with injectables in the hope that the HAE attack will dissipate on its own, which leads to delayed (or even no) treatment. This can lead to more severe attacks, longer recovery time and the need for more serious medical intervention. There is therefore a particular need for an effective treatment of severe and very severe attacks, which is a problem addressed by the present invention.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or

solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is a severe or worse HAE attack. In particular, the invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

PGI-S is a known scale in the art (see e.g. Allergy Asthma Proc. 2018 Jan 1;39(1):74-80. Doi: 10.2500/aap.2018.39.4095) that can be used to report the severity of HAE attacks and for example can be used to report attacks as “none”, “mild”, “moderate”, “severe” or “very severe”.

Where appropriate, any of the treatments described herein can be for treating an HAE attack that is characterised as “severe” or above according to the PGI-S scale. Specific embodiments are as follows.

Specific treatments of severe or worse HAE attacks

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale. In an embodiment, the first dose is administered on-demand within 1 hour of recognition of a symptom of an acute HAE attack. In another embodiment, the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised. In an embodiment, a second dose is not administered to the patient, e.g., where the first dose provides sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a second dose to the patient.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose

of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). In an embodiment, the second dose is administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the first dose. Preferably, the second dose is administered
5 about 3 hours after the first dose.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or
10 above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.

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In an embodiment, a third dose is not administered to the patient, e.g., where the first dose and second dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a third dose to the patient. In an alternative embodiment, the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
20 The third dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the second dose. Preferably, the third dose can be administered about 3 hours after the second dose.

25 The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose
30 of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate
35 thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or

above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof),
5 wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose.

In an embodiment, a fourth dose is not administered to the patient, e.g., where the first dose, second
10 dose and third dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a fourth dose to the patient. In an alternative embodiment, the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The fourth dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours,
15 between 2 hours and about 3 hours) after the third dose. Preferably, the fourth dose can be administered about 3 hours after the third dose.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate
20 thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)
25 followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate
30 thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)
35 followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or

solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose.

In an embodiment, no further dose is administered to the patient, e.g., the attack is resolved without administering any further dose to the patient, in particular, no fifth dose is administered.

In any of the above embodiments, each dose is preferably administered as one unit dose. In particular, each unit dose is preferably administered as one tablet (e.g. a film-coated tablet or an orodispersible tablet).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as "severe" or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE. In an embodiment, the HAE attack is characterised as "severe" according to the PGI-S scale. In another embodiment, the HAE attack is characterised as "very severe" according to the PGI-S scale.

The prophylactic treatment of HAE can be a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.

The prophylactic treatment of HAE can be a PKa binding agent, preferably a plasma kallikrein inhibitor.

The prophylactic treatment of HAE can be a bradykinin B2 receptor antagonist.

The prophylactic treatment of HAE can be a Factor XIIa (FXIIa) binding agent, preferably a FXIIa inhibitor.

The prophylactic treatment of HAE can be attenuated androgen. In particular, the attenuated androgen can be danazol or oxandrolone. The prophylactic treatment of HAE can be tranexamic acid. Alternatively, the prophylactic treatment of HAE can be non-androgen therapy.

The prophylactic treatment of HAE can be selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen,
5 and deucricitibant.

The prophylactic treatment of HAE can be C1 inhibitor. In particular, the prophylactic treatment can be Cinryze®, Haegarda®, or Berinert®.

10 The prophylactic treatment can be lanadelumab or berotralstat.

The prophylactic treatment can be lanadelumab.

The prophylactic treatment can be berotralstat.

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The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic
20 treatment of HAE, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic
25 treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE
30 attack is characterised as “very severe” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or
35 above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic

treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®). In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate

thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is
5 characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or
10 above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®). In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment
20 of HAE and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®),
25 donidalorsen, and deucricitibant, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

20 The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

30 The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe”

according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand
5 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), and wherein the attack is resolved without administering a second dose to the
10 patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

Alternatively, the invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or
15 solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is not also being treated with a prophylactic treatment of HAE. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being
25 treated with a prophylactic treatment of HAE. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand
30 comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In
35 another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
5 is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from
15 lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE
20 attack is characterised as “very severe” according to the PGI-S scale.

The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
25 is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®). In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being
35 treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from

lanadelumab and berotralstat. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

- 5 The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab. In an
10 embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

- The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically
15 acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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- The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is also being
25 treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®). In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

- 30 Alternatively, the invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the patient is not also being treated with a prophylactic treatment of HAE. In an embodiment, the HAE attack is

characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

In any of the above embodiments, the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an abdominal attack, a subcutaneous attack, an attack of the arms, an attack of the hands, an attack of the legs, an attack of the feet, an attack of the head, an attack of the face, an attack of the neck, an attack of the torso, and an attack of the genitals. In an embodiment, the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is an attack of the neck and above. In an embodiment, the HAE attack is an attack of the neck and above but is not a laryngeal attack. In an embodiment, the HAE attack is an abdominal attack. In an embodiment, the HAE attack is a subcutaneous attack. In an embodiment, the HAE attack is an attack of the arms. In an embodiment, the HAE attack is an attack of the hands. In an embodiment, the HAE attack is an attack of the legs. In an embodiment, the HAE attack is an attack of the feet. In an embodiment, the HAE attack is an attack of the head. In an embodiment, the HAE attack is an attack of the face. In an embodiment, the HAE attack is an attack of the neck. In an embodiment, the HAE attack is an attack of the torso. In an embodiment, the HAE attack is an attack of the genitals.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale and wherein the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale and wherein the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an attack of the neck and above.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an attack of the neck and above.

thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an abdominal attack.

5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is a subcutaneous attack.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack.

15 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is a laryngeal attack.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack

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is characterised as “moderate” or above according to the PGI-S scale, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an attack of the neck and above.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an abdominal attack.

15

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is a subcutaneous attack.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack.

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For the avoidance of doubt, any of the embodiments described above in relation to the treatment of severe or worse HAE attacks according to the invention can, where appropriate, be considered in combination with any of the embodiments described below in relation to the treatment of HAE attacks in patients on prophylactic treatment, dosing, the treatment of HAE attacks of the neck and above, specific combination therapies and drug-drug interactions. It is intended that any of the embodiments can be combined.

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Treatment of HAE attacks in patients on prophylactic treatment

As noted above, existing treatments of HAE are either administered on-demand or as a prophylactic. On-demand treatment is administered in response to a specific attack to lessen its severity e.g., at the first sign of attack symptoms. Prophylactic treatment involves continuously and regularly taking treatment to reduce the likelihood of an attack occurring i.e. not in response to one specific attack.

The overarching goal of long-term prophylactic treatment is to achieve an attack-free status. However, existing prophylactic treatments are generally not completely effective, with patients receiving prophylactic treatment still suffering from HAE attacks. This is demonstrated by the attack incidences data taken from patients on prophylactic treatment that are reported in Example 4 and in Figures 2 and 3. For this reason, it is generally recommended that HAE patients carry an on-demand treatment at all times even if they are on prophylactic treatment (such treatment can sometimes be called a “rescue treatment”). In fact, the approved labels for both Takhzyro® and Orladeyo® recommend that a patient carry a rescue treatment in the case of an HAE attack. Patients on prophylactic treatment therefore still face the risk of having an attack and continue to experience burden in their day-to-day life, largely due to the challenges associated with current parenteral on-demand therapies, as described above.

In particular, the location, duration and severity of attacks are similar between patients receiving prophylactic treatment and patients who are taking on-demand treatment only (see Figures 2 and 3, which shows the distribution of attack severity (PGI-S) at baseline in the Phase 3 clinical trial investigating sebetralstat, the results of which are reported herein). Notably, patients on prophylactic treatment still experience severe and very severe attacks, regardless of the use of prophylaxis (see also Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. Allergy. 2022; 77: 1961–1990. doi:10.1111/all.15214). Accordingly, all HAE patients, regardless of their current treatment regime (or lack thereof) would benefit from having effective on-demand treatments of HAE, which is a need addressed by the present invention.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE.

The invention provides sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) for use in treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first

dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE.

- 5 The invention provides a prophylactic treatment of HAE for use in treating hereditary angioedema (HAE), wherein the patient is orally administered a first dose of 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) on-demand for treating an attack of HAE on-demand.

10 The invention provides sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) and a prophylactic treatment of HAE for use in treating hereditary angioedema (HAE) in a patient in need thereof comprising: administering the prophylactic treatment of HAE to the patient and orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) for treating an attack of HAE on-demand.

- 15 For the avoidance of doubt, any of the embodiments described above in relation to the treatment of severe or worse HAE attacks according to the invention, or below in relation to dosing, the treatment of HAE attacks of the neck and above, specific combination therapies and drug-drug interactions can, where appropriate, be considered in combination with any of embodiments described herein relation to treatment of HAE attacks in patients on prophylactic treatment. It is intended that any of the
20 embodiments can be combined.

Therefore, where appropriate, any of the treatments described herein can therefore be for treating an HAE attack wherein the patient is also being treated with a prophylactic treatment of HAE. Specific embodiments are as follows.

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Specific treatments of HAE attacks in patients on prophylactic treatment

- In any of the embodiments described herein, sebetralstat and the prophylactic treatment of HAE can be administered simultaneously, separately or sequentially. For the avoidance of doubt, sebetralstat and the
30 prophylactic treatment of HAE are not necessarily given at the same time, i.e., sebetralstat and the prophylactic treatment of HAE can be given at different times of the day. Indeed, this would be expected because a patient would typically take their prophylactic treatment at a particular time, whereas the on-demand treatment would be used as necessary upon recognition of a HAE attack.

In any of the embodiments described herein, the first dose can be administered on-demand within 1 hour of recognition of a symptom of an acute HAE attack. In another embodiment, the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, within about 6 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised. In an embodiment, a second dose is not administered to the patient, e.g., where the first dose provides sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a second dose to the patient.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). In an embodiment, the second dose is administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the first dose. Preferably, the second dose is administered about 3 hours after the first dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.

In an embodiment, a third dose is not administered to the patient, e.g., where the first dose and second dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a third dose to the patient. In an alternative embodiment, the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The third dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about

3 hours) after the second dose. Preferably, the third dose can be administered about 3 hours after the second dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose.

In an embodiment, a fourth dose is not administered to the patient, e.g., where the first dose, second dose and third dose provide sufficient therapeutic effectiveness, for example, the attack is resolved without administering a fourth dose to the patient. In an alternative embodiment, the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The fourth dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the third dose. Preferably, the fourth dose can be administered about 3 hours after the third dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of

sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose.

In an embodiment, no further dose is administered to the patient, e.g., the attack is resolved without administering any further dose to the patient, in particular, no fifth dose is administered.

In any of the above embodiments, each dose is preferably administered as one unit dose. In particular, each unit dose is preferably administered as one tablet (e.g. a film-coated tablet or an orodispersible tablet).

In any of the above embodiments, the prophylactic treatment of HAE can be a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.

The prophylactic treatment of HAE can be a PKa binding agent, preferably a plasma kallikrein inhibitor.

The prophylactic treatment of HAE can be a bradykinin B2 receptor antagonist.

The prophylactic treatment of HAE can be a Factor XIIa (FXIIa) binding agent, preferably a FXIIa inhibitor.

The prophylactic treatment of HAE can be attenuated androgen. In particular, the attenuated androgen can be danazol or oxandrolone. The prophylactic treatment of HAE can be tranexamic acid. Alternatively, the prophylactic treatment of HAE can be non-androgen therapy.

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The prophylactic treatment of HAE can be selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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The prophylactic treatment of HAE can be C1 inhibitor. In particular, the prophylactic treatment can be Cinryze®, Haegarda®, or Berinert®.

15 The prophylactic treatment can be lanadelumab or berotralstat.

The prophylactic treatment can be lanadelumab.

The prophylactic treatment can be berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a Factor Xlla (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is a Factor Xlla (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of

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about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is a plasma kallikrein inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is a plasma kallikrein inhibitor.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is a plasma kallikrein inhibitor.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is a plasma kallikrein inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of

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about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is a plasma kallikrein inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is a plasma kallikrein inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the

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prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a

prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof),
5 wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and
10 deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
15 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a
20 third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected
25 from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate
30 thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)
35 followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or

solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of

about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is lanadelumab.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of

about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is lanadelumab.

- 5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of
10 about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is lanadelumab.

- The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
15 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a
20 third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is lanadelumab.

- 25 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of
30 sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is lanadelumab.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is lanadelumab.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the

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second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of

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about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)

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followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

- 5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of
- 10 about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered
- 15 between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose, and wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).
- 20 In any of the above embodiments, the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an abdominal attack, a subcutaneous attack, an attack of the arms, an attack of the hands, an attack of the legs, an attack of the feet, an attack of the head, an attack of the face, an attack of the neck, an attack of the torso, and an attack of the genitals. In an embodiment, the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is an attack of the neck and above. In an embodiment, the HAE
- 25 attack is an attack of the neck and above but is not a laryngeal attack. In an embodiment, the HAE attack is an abdominal attack. In an embodiment, the HAE attack is a subcutaneous attack. In an embodiment, the HAE attack is an attack of the arms. In an embodiment, the HAE attack is an attack of the hands. In an embodiment, the HAE attack is an attack of the legs. In an embodiment, the HAE attack is an attack of the feet. In an embodiment, the HAE attack is an attack of the head. In an embodiment, the HAE attack is an
- 30 attack of the face. In an embodiment, the HAE attack is an attack of the neck. In an embodiment, the HAE attack is an attack of the torso. In an embodiment, the HAE attack is an attack of the genitals.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or

solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a laryngeal attack.

5 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a laryngeal attack.

10 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and wherein the HAE attack is a laryngeal attack.

15 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab and wherein the HAE attack is a laryngeal attack.

20 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and wherein the HAE attack is a laryngeal attack.

25 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab and wherein the attack is resolved without administering a second dose to the patient.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and wherein the attack is resolved without administering a second dose to the patient.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and wherein the attack is resolved without administering a second dose to the patient.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab and wherein the attack is resolved without administering a second dose to the patient.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a

pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and wherein the attack is resolved without administering a second dose to the patient.

- 5 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and wherein the
10 attack is resolved without administering a second dose to the patient.

- The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein
15 the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, and wherein the attack is resolved without administering a second dose to the patient.

- The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a
20 pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above.

- The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a
25 pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an abdominal attack.

- 30 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a subcutaneous attack. In an embodiment, the prophylactic treatment is selected from lanadelumab,
35 berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein
5 the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and wherein the HAE attack is a subcutaneous attack.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a
10 pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab and wherein the HAE attack is a subcutaneous attack.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a
15 pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and wherein the HAE attack is a subcutaneous attack.

20 In any of the above embodiments, the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.
25 Preferably, the HAE attack is characterised as “severe” or above according to the PGI-S scale. In particular, the HAE attack is characterised as “severe” or “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a
30 pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and the HAE attack is characterised as “mild” or above according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE)
35 on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a

pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and the HAE attack is characterised as “mild” according to the PGI-S scale. In an embodiment, the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab and the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and the HAE attack is characterised

as “moderate” according to the PGI-S scale. In an embodiment, the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

- 5 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat and the HAE attack is characterised as “moderate” according to the PGI-S scale.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment

- 15 is lanadelumab and the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein

20 the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®) and the HAE attack is characterised as “moderate” according to the PGI-S scale.

- The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very
- 25
- 30 severe” according to the PGI-S scale.

- The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is
- 35 also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as

“mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

5 The invention provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

30 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein

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the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is a laryngeal attack, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale, and wherein the attack is resolved without administering a second dose to the patient. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “moderate” or above according to

the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a

pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “severe” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “very severe” according to the PGI-S scale.

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Dosing

Given the serious nature of HAE attacks, and that they can increase in severity such that they can be life-threatening, it is important that any on-demand treatment provides reliably safe and effective treatment. The data in Example 4 further confirm that particular dosage regimens of sebetralstat provide such reliable treatment.

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The invention therefore also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

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For the avoidance of doubt, any of the embodiments described above in relation to the treatment of severe or worse HAE attacks according to the invention or to the treatment of HAE attacks in patients on prophylactic treatment, or below in relation to the treatment of HAE attacks of the neck and above, specific combination therapies and drug-drug interactions can, where appropriate, be considered in combination with any of the embodiments described herein in relation to dosing. It is intended that any of the embodiments can be combined. Specific embodiments are as follows.

Specific dosing regimens

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In an embodiment, the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack. In another embodiment, the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, within about 6 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.

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In an embodiment, the second dose is administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the first dose. Preferably, the second dose is administered about 3 hours after the first dose.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.

25

In an embodiment, a third dose is not administered to the patient, e.g., where the first dose and second dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a third dose to the patient. In an alternative embodiment, the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The third dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about

30

35

3 hours) after the second dose. Preferably, the third dose can be administered about 3 hours after the second dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose.

In an embodiment, a fourth dose is not administered to the patient, e.g., where the first dose, second dose and third dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a fourth dose to the patient. In an alternative embodiment, the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The fourth dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the third dose. Preferably, the fourth dose can be administered about 3 hours after the third dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second

dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second
10 dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third
15 dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose.

In an embodiment, no further dose is administered to the patient, e.g., the attack is resolved without
20 administering any further dose to the patient, in particular, no fifth dose is administered.

In any of the above embodiments, each dose is preferably administered as one unit dose. In particular, each unit dose is preferably administered as one tablet (e.g. a film-coated tablet or an orodispersible tablet).

25

In any of the embodiments described herein, the patient can also be being treated with a prophylactic treatment of HAE. Specific embodiments wherein the patient is also being treated with a prophylactic treatment of HAE are described above.

30 In any of the above embodiments, the prophylactic treatment of HAE can be a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.

The prophylactic treatment of HAE can be a PKa binding agent, preferably a plasma kallikrein inhibitor.

35 The prophylactic treatment of HAE can be a bradykinin B2 receptor antagonist.

The prophylactic treatment of HAE can be a Factor XIIa (FXIIa) binding agent, preferably a FXIIa inhibitor.

5 The prophylactic treatment of HAE can be attenuated androgen. In particular, the attenuated androgen can be danazol or oxandrolone. The prophylactic treatment of HAE can be tranexamic acid. Alternatively, the prophylactic treatment of HAE can be non-androgen therapy.

10 The prophylactic treatment of HAE can be selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

15 In another embodiment, the prophylactic treatment of HAE is C1 inhibitor. In particular, the prophylactic treatment can be Cinryze®, Haegarda®, or Berinert®.

The prophylactic treatment can be lanadelumab or berotralstat.

20 The prophylactic treatment can be lanadelumab.

The prophylactic treatment can be berotralstat.

25 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

30 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of
35 about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the

second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is not also being treated with a

prophylactic treatment of HAE, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose.

In any of the above embodiments, the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an abdominal attack, a subcutaneous attack, an attack of the arms, an attack of the hands, an attack of the legs, an attack of the feet, an attack of the head, an attack of the face, an attack of the neck, an attack of the torso, and an attack of the genitals. In an embodiment, the HAE attack is a laryngeal attack. In an embodiment, the HAE attack is an attack of the neck and above. In an embodiment, the HAE attack is an attack of the neck and above but is not a laryngeal attack. In an embodiment, the HAE attack is an abdominal attack. In an embodiment, the HAE attack is a subcutaneous attack. In an embodiment, the HAE attack is an attack of the arms. In an embodiment, the HAE attack is an attack of the hands. In an embodiment, the HAE attack is an attack of the legs. In an embodiment, the HAE attack is an attack of the feet. In an embodiment, the HAE attack is an attack of the head. In an embodiment, the HAE attack is an attack of the face. In an embodiment, the HAE attack is an attack of the neck. In an embodiment, the HAE attack is an attack of the torso. In an embodiment, the HAE attack is an attack of the genitals.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second

dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is an abdominal attack.

5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is a subcutaneous attack.

10

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second
15 dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the HAE attack is a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
20 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose,
25 preferably about 3 hours after the first dose, and wherein the HAE attack is an abdominal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
30 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the HAE attack is a subcutaneous attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second
5 dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
10 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or
15 solvate thereof), and wherein the HAE attack is an abdominal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
20 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is a subcutaneous attack.

25 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)
30 followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the HAE attack is a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second
5 dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the
10 second dose, and wherein the HAE attack is an abdominal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
15 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered
20 between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the HAE attack is a subcutaneous attack.

In any of the above embodiments, the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale. In
25 another embodiment, the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale. Preferably, the HAE attack is characterised as “severe” or above according to the PGI-S scale. In particular, the HAE attack is characterised as “severe” or “very severe” according to the PGI-S scale.

30 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and
35 wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as "mild" according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as "moderate" or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as "moderate" according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as "mild" or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetrastat (or a pharmaceutically acceptable salt and/or solvate thereof),

wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “mild”
10 or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
15 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

20 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof),
25 wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
30 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second
5 dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a laryngeal attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
10 comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is an abdominal attack, and wherein the HAE attack is characterised as “severe”
15 or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about
20 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the HAE attack is a subcutaneous attack, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

25 *Treatment of HAE attacks of the neck and above*

As noted above, patients with HAE experience unpredictable and often debilitating attacks of tissue swelling that can affect any part of the body and be critical if the upper airways are affected. HAE attacks that begin at the neck and above can lead to laryngeal attacks which can be life-threatening if not treated
30 early. Therefore, it is of paramount importance that on-demand treatments of attacks of the neck and above are effective. In particular, treatment must be fast-acting and provide early intervention to shorten the duration and severity of the attack and lead to faster attack resolution. The barriers associated with current on-demand parenteral therapies means that patients often delay treatment and therefore there is a continued need to provide patients with the confidence that alternative (i.e., non-injectable) therapies
35 will provide effective treatment of attacks of the neck and above.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein
5 the HAE attack is an attack of the neck and above.

For the avoidance of doubt, any of the embodiments described above in relation to the treatment of severe or worse HAE attacks, treatment of HAE attacks in patients on prophylactic treatment, or dosing, or below in relation to specific combination therapies and drug-drug interactions can, where appropriate,
10 be considered in combination with any of the embodiments described herein relation to treatment of HAE attacks of the neck and above. It is intended that any of the embodiments can be combined.

Therefore, where appropriate, any of the treatments described herein can be for treating an HAE attack of the neck and above. Specific embodiments are as follows.

15

Specific treatments of HAE attacks of the neck and above

The attack of the neck and above can be a facial attack (i.e., an attack of the face) and/or an attack of the tongue and/or an attack of the throat. The attack of the neck and above can be a facial attack. The attack
20 of the neck and above can be an attack of the tongue. The attack of the neck and above can be an attack of the throat. The attack of the neck and above can be a laryngeal attack. The attack of the neck and above can be an attack of the throat, and/or the tongue, and/or face. The attack of the neck and above can be an attack of the tongue, and/or the throat, and/or face. The attack of the neck and above can be an attack of the face, and/or the throat, and/or the throat. The attack of the neck and above is an attack of the
25 throat but is not a laryngeal attack.

In any of the above embodiments, the first dose can be administered on-demand within 1 hour of recognition of a symptom of an acute HAE attack. In another embodiment, the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20
30 minutes, within about 10 minutes, within about 6 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised. In an embodiment, a second dose is not administered to the patient, e.g., where the first dose provides sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a second dose to the patient.

In an embodiment, the attack of the neck and above is a laryngeal attack and the attack is resolved without administering a second dose to the patient.

5 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, wherein the attack of the neck and above is a laryngeal attack and the attack is resolved without administering a second dose to the patient.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of
15 sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). In an embodiment, the second dose is administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the first dose. Preferably, the second dose is administered about 3 hours after the first dose.

20 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of
25 sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.

In an embodiment, a third dose is not administered to the patient, e.g., where the first dose and second
30 dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a third dose to the patient. In an alternative embodiment, the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The third dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about

3 hours) after the second dose. Preferably, the third dose can be administered about 3 hours after the second dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose.

In an embodiment, a fourth dose is not administered to the patient, e.g., where the first dose, second dose and third dose provide sufficient therapeutic effectiveness, for example, the attack can be resolved without administering a fourth dose to the patient. In an alternative embodiment, the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The fourth dose can be administered between about 2 hours and about 6 hours (more specifically, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between 2 hours and about 3 hours) after the third dose. Preferably, the fourth dose can be administered about 3 hours after the third dose.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a

pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose.

20 In an embodiment, no further dose is administered to the patient, e.g., the attack is resolved without administering any further dose to the patient.

In any of the above embodiments, each dose is preferably administered as one unit dose. In particular, each unit dose is preferably administered as one tablet (e.g. a film-coated tablet or an orodispersible tablet).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and

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above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE.

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15 In any of the above embodiments, the prophylactic treatment of HAE can be a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.

The prophylactic treatment of HAE can be a PKa binding agent, preferably a plasma kallikrein inhibitor.

20 The prophylactic treatment of HAE can be a bradykinin B2 receptor antagonist.

The prophylactic treatment of HAE can be a Factor XIIa (FXIIa) binding agent, preferably a FXIIa inhibitor.

The prophylactic treatment of HAE can be attenuated androgen. In particular, the attenuated androgen can be danazol or oxandrolone. The prophylactic treatment of HAE can be tranexamic acid. Alternatively, the prophylactic treatment of HAE can be non-androgen therapy.

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The prophylactic treatment of HAE can be selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 30 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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In another embodiment, the prophylactic treatment of HAE is C1 inhibitor. In particular, the prophylactic treatment can be Cinryze®, Haegarda®, or Berinert®.

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The prophylactic treatment can be lanadelumab or berotralstat.

The prophylactic treatment can be lanadelumab.

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The prophylactic treatment can be berotralstat.

10 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

15 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is
20 also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours
25 after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
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is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically

acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and

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above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is lanadelumab.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a

pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE,
5 wherein the prophylactic treatment is lanadelumab.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
10 is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is
20 berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE,
30 wherein the prophylactic treatment is berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
35 is an attack of the neck and above, and wherein the patient is also being treated with a prophylactic

treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is
10 also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is
15 administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is also being treated with a prophylactic treatment of HAE, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack
25 is an attack of the neck and above, and wherein the patient is not also being treated with a prophylactic treatment of HAE.

30 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of

sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the patient is not also being treated with a prophylactic treatment of HAE.

5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is
10 administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the patient is not also being treated with a prophylactic treatment of HAE.

In any of the above embodiments, the HAE attack is characterised as “mild” or above according to the
15 PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “moderate” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale. Preferably, the HAE attack is characterised as “severe” or above according to the PGI-S scale. In particular, the HAE attack is characterised as “severe” or “very severe” according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “severe” or above
25 according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and
30 above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

Specific treatments of HAE attacks of the neck and above that are not laryngeal attacks

An attack of the neck and above that is not a laryngeal attack can readily progress into a laryngeal attack, which can be life threatening. It is advantageous to treat such attacks to slow the progression into a laryngeal attack. It is advantageous to treat such attacks to reduce the severity of any resulting laryngeal attack. It is advantageous to treat such attacks to prevent the attack from progressing or spreading into a laryngeal attack. Where appropriate, any of the treatments described herein can therefore be for treating an attack of the neck and above that is not a laryngeal attack. Specific embodiments are as follows.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically

acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of

about 300mg of (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and wherein the attack of the neck and above is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is an attack of the neck and above, and wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose, preferably about 3 hours after the second dose, and wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose, preferably about 3 hours after the third dose and wherein the attack of the neck and above is not a laryngeal attack.

In any of the above embodiments wherein the attack of the neck and above is not a laryngeal attack, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) slows the progression of the attack into a laryngeal attack. In another embodiment wherein the attack of the neck and above is not a laryngeal attack, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) reduces the

severity of any resulting laryngeal attack. In another embodiment wherein the attack of the neck and above is not a laryngeal attack, prevents the attack from progressing into a laryngeal attack.

Specific combination therapies

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As mentioned above, the data described herein show that sebetralstat (a plasma kallikrein inhibitor) can be used on-demand to treat HAE attacks in patients who are also being treated with a prophylactic HAE treatment (even when the prophylactic treatment is also a plasma kallikrein inhibitor), in particular where the HAE attack is a severe or very severe attack and/or where the HAE attack is an attack of the neck and above but is not a laryngeal attack. The attack of the neck and above can be a facial attack (i.e., an attack of the face) and/or an attack of the tongue and/or an attack of the throat. It is important that a broad range of HAE patients and a wide range of HAE attacks can benefit from on-demand treatment.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack.

The attack of the neck and above can be a facial attack and/or an attack of the throat and/or an attack of the tongue.

Any of the embodiments described above in relation to in relation to the treatment of severe or worse HAE attacks, treatment of HAE attacks in patients on prophylactic treatment, or dosing, or below in relation to drug-drug interactions can, where appropriate, be considered in combination with any of the embodiments described herein relation to specific combination therapies. It is intended that any of the embodiments can be combined.

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Specific combination therapies are as follows.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof
5 on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof
10 on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “very severe” according to the PGI-S scale.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof
15 on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, and wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an abdominal attack, and a subcutaneous attack.

20 The HAE attack can be a laryngeal attack. The HAE attack can be an attack of the neck and above. The HAE attack can be an abdominal attack. The HAE attack can be a subcutaneous attack. The HAE attack can be an attack of the neck and above but is not a laryngeal attack.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand
25 comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “mild” according to the PGI-S scale. In another embodiment, the HAE attack is characterised as “moderate” or
30 above according to the PGI-S scale. In an embodiment, the HAE attack is characterised as “moderate” according to the PGI-S scale. Preferably, the HAE attack is characterised as “severe” or above according to the PGI-S scale. In particular, the HAE attack is characterised as “severe” or “very severe” according to the PGI-S scale.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein the HAE attack is characterised as
5 “severe” or above according to the PGI-S scale.

In any of the above embodiments, the prophylactic treatment of HAE can be a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.

10 The prophylactic treatment of HAE can be a PKa binding agent, preferably a plasma kallikrein inhibitor. The data in Example 4 show that sebetralstat (a plasma kallikrein inhibitor) is safe and effective at treating HAE attacks even when the patient is already taking a different plasma kallikrein inhibitor as a prophylactic treatment (specifically, lanadelumab or berotralstat). This is advantageous and demonstrates the usefulness and a reliability of sebetralstat (a plasma kallikrein inhibitor) in a wide range of relevant clinical
15 circumstances e.g. even when a patient is taking a plasma kallikrein inhibitor prophylactic treatment.

The prophylactic treatment of HAE can be a bradykinin B2 receptor antagonist.

The prophylactic treatment of HAE can be a Factor XIIa (FXIIa) binding agent, preferably a FXIIa inhibitor.
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The prophylactic treatment of HAE can be attenuated androgen. In particular, the attenuated androgen can be danazol or oxandrolone. The prophylactic treatment of HAE can be tranexamic acid. Alternatively, the prophylactic treatment of HAE can be non-androgen therapy.

25 The prophylactic treatment of HAE can be selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant. In an embodiment, the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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The prophylactic treatment of HAE can be C1 inhibitor. In particular, the prophylactic treatment can be Cinryze®, Haegarda®, or Berinert®.

The prophylactic treatment can be lanadelumab or berotralstat.

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The prophylactic treatment can be lanadelumab.

The prophylactic treatment can be berotralstat.

- 5 The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is a Factor

15 XIIa (FXIIa) inhibitor.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein

20 the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein

25 the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is a plasma kallikrein inhibitor.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE)

30 on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is selected
5 from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitabant.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof
10 on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is selected from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

15 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is selected
20 from lanadelumab, berotralstat, and C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof
25 on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein
30 the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.

The invention therefore provides a method for treating an attack of hereditary angioedema (HAE)
35 on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof

on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is lanadelumab.

- 5 The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is lanadelumab.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is berotralstat.

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is berotralstat.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, wherein the prophylactic treatment is C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®).

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Drug-drug interactions

The data disclosed herein demonstrate that a drug-drug interaction occurs when sebetralstat (or pharmaceutically acceptable salt and/or solvate thereof) is administered with a strong or moderate
5 CYP3A4 inhibitor or a CYP3A4 inducer. In particular, concomitant administration of a strong or moderate CYP3A4 inhibitor or a strong or moderate CYP3A4 inducer affects the blood levels of sebetralstat (or pharmaceutically acceptable salt and/or solvate thereof).

Concomitant administration of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof)
10 and a CYP3A4 inhibitor has the potential to increase or prolong the effects of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). Concomitant administration of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) and a CYP3A4 inducer has the potential to decrease or shorten the effects of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). It may be desirable to account for these interactions with adequate dose adjustments.

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The invention therefore provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will take, a concomitant dose of a strong or moderate CYP3A4 inhibitor and wherein the method comprises reducing
20 the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will take, a
25 concomitant dose of a strong or moderate CYP3A4 inducer and wherein the method comprises increasing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

For the avoidance of doubt, any of the embodiments described above in relation to the treatment of severe or worse HAE attacks, treatment of HAE attacks in patients on prophylactic treatment, dosing, the
30 treatment of HAE attacks of the neck and above, or specific combination therapies can, where appropriate, be considered in combination with any of the embodiments described herein relation to drug-drug interactions. It is intended that any of the embodiments can be combined.

Concomitant administration can mean that the sebetralstat and the CYP3A4 inhibitor/inducer are
35 administered simultaneously, separately or sequentially. For the avoidance of doubt, sebetralstat and the

CYP3A4 inhibitor/inducer are not necessarily given at the same time, i.e., sebetralstat and the CYP3A4 inhibitor/inducer can be given at different times of the day.

As used in the context of this drug-drug interaction section, a “strong CYP3A4 inhibitor” is a drug that increases the AUC of sensitive index substrates of a given metabolic pathway ≥ 5 -fold. As used herein, a “moderate CYP3A4 inhibitor” is a drug that increases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 2 - to < 5 -fold. As used herein, a “strong CYP3A4 inducer” is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80 percent. As used herein, a “moderate CYP3A4 inducer” is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 50 percent to < 80 percent. These definitions are in accordance with the FDA definition (<https://www.fda.gov/media/134581/download> - see pages 23-24) and the EMA definition (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf - see Appendix VIII).

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Specific treatments to account for potential drug-drug interactions

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will take, a concomitant dose of a strong or moderate CYP3A4 inhibitor and wherein the method comprises reducing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) so as to diminish the additive effect experienced when co-administered with the strong or moderate CYP3A4 inhibitor. In an embodiment, the additive effect is an increased therapeutic effect of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

In any of the above embodiments, the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 10% to about 60% of the normal dose for the patient. The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 20% to about 50% of the normal dose for the patient. The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 30% to about 50% of the normal dose for the patient. The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 40% to about 50% of the normal dose for the patient. In particular, the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 50% of the normal dose for the patient.

In any of the above embodiments, the “normal dose” for the patient is preferably 300mg.

In some embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. The strong CYP3A4 inhibitor can be selected from itraconazole, ketoconazole, ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, lopinavir and ritonavir, clarithromycin, ceritinib, cobicistat, idelalisib, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, saquinavir and ritonavir, telithromycin, tipranavir and ritonavir, voriconazole, darunavir, telaprevir, stiripentol, curcumin, troleandomycin, atazanavir, naloxone, nilotinib, delavirdine, loperamide, ribociclib, danoprevir, midostaurin, terfenadine, ergotamine, econazole, ditiocarb, methimazole, boceprevir, lonafarnib, amprenavir, amiodarone, and levoketoconazole.

In other embodiments, the CYP3A4 inhibitor is a moderate CYP3A4 inhibitor. The moderate CYP3A4 inhibitor can be selected from verapamil, aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, erythromycin, fluconazole, grapefruit juice, imatinib, isavuconazole, isavuconazonium, luliconazole, netupitant, miconazole, nicardipine, isoniazid, danazol, lovastatin, ziprasidone, desvenlafaxine, indalpine, zimelidine, milnacipran, fusidic acid, barnidipine, benidipine, isradipine, haloperidol, linagliptin, fosnetupitant, simeprevir, nilvadipine, primaquine, clozapine, tioconazole, venetoclax, seproxetine, fluvoxamine, fosamprenavir, cyclosporine, abiraterone, clindamycin, berotralstat, tepotinib, and lenacapavir.

The invention also provides a method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will take, a concomitant dose of a strong or moderate CYP3A4 inducer and wherein the method comprises increasing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) so as to compensate for the effect experienced during co-administration. In an embodiment, the effect experienced during co-administration is a decreased therapeutic effect of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

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In any of the above embodiments, the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 10% to about 60% of the normal dose for the patient. The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 20% to about 50% of the normal dose for the patient. The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 30% to about 50% of the normal dose for the patient.

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The dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 40% to about 50% of the normal dose for the patient. In particular, the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 50% of the normal dose for the patient.

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In any of the above embodiments, the “normal dose” for the patient is preferably 300mg.

In some embodiments, the CYP3A4 inducer is a strong CYP3A4 inducer. The strong CYP3A4 inducer can be selected from 3-phenytoin, fosphenytoin, apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor and ivacaftor, mitotane, rifampin, St. John’s wort, pentobarbital, phenobarbital, enzalutamide, rimexolone, rifaximin, rifamycin, midostaurin, dexamethasone, and rifapentine.

In other embodiments, the CYP3A4 inducer is a moderate CYP3A4 inducer. The moderate CYP3A4 inducer can be selected from efavirenz, bosentan, cenobamate, dabrafenib, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib, modafinil, nafcillin, bexarotene, avasimibe, echinacea, dexamethasone, and dexamethasone acetate.

Further embodiments that apply to any of the treatments described herein

In any of the treatments of the invention described herein, sebetralstat is orally administered in a therapeutically effective amount. Unless stated otherwise, the therapeutically effective amount can be between about 100 mg and about 1500 mg, about 300 mg and about 1800 mg, about 100 mg and about 1400 mg, about 200 mg and about 1200 mg, about 300 mg and about 1200 mg, about 600 mg and about 1200 mg, about 450 mg and about 900 mg, about 500 mg and about 1000 mg, about 450 mg and about 600 mg, about 500 mg and about 700 mg (more specifically, 600 mg), about 800 mg and about 1000 mg per day, about 900 mg and about 1400 mg (more specifically 1200 mg), or about 900 mg and about 1200 mg. The therapeutically effective amount can be between about 250 mg and about 350 mg, between about 270 mg and about 330 mg, between about 275 mg and about 325 mg, between about 285 mg and about 315 mg, between about 290 mg and about 310 mg, or between about 295 mg and about 305 mg. Preferably the therapeutically effective amount is about 300 mg. As used herein, “about” means $\pm 10\%$.

In any of the embodiments described herein, the sebetralstat is preferably in the free base form.

In any of the embodiments described herein, the patient can be aged 12 years and above. In particular, the patient can be aged between 12 and less than 18. Alternatively, the patient can be aged 18 years and above.

- 5 In any of the embodiments described herein, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief. The term “symptom relief” in this context can mean that the attack is rated as “a little better” or higher for two consecutive time points when assessed according to the PGI-C scale. PGI-C is a known index in the art that can be used to score the progression of an HAE attack and to report attacks as “much better”, “better”, “a little better”,
10 “no change”, “a little worse”, “worse”, or “much worse”.

When assessed using the PGI-C scale, in any of the treatments of the invention, sebetralstat is administered to reduce the time to beginning of symptom relief to between about 0.7 and about 8 hours after the first dose of sebetralstat. Symptom relief can start between about 1 and about 8 hours after the
15 first dose. Symptom relief can start between about 1 and about 6 hours after the first dose of sebetralstat. Symptom relief can start between about 1 and about 4 hours after the first dose of sebetralstat. Symptom relief can start between about 1 and about 2 hours after the first dose. Symptom relief can start between about 1.5 and about 1.8 hours after the first dose. Symptom relief can start at about 1.61 hours after the first dose of sebetralstat.

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In any of the embodiments described herein, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity. The term “reduction in attack severity” in this context can mean that the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.

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When assessed using the PGI-S scale, in any of the treatments of the invention, sebetralstat is administered to reduce the time to a reduction in attack severity to between about 1 and about 12 hours. Reduction in attack severity can start between about 2 and about 11 hours. Reduction in attack severity can start between about 3 and about 10 hours. Reduction in attack severity can start between about 5
30 and about 10 hours. Reduction in attack severity can start between about 9 and about 10 hours. Reduction in attack severity can start between about 9 and about 9.5 hours. Reduction in attack severity can start at about 9.27 hours.

In any of the embodiments described herein, sebetralstat (or a pharmaceutically acceptable salt and/or
35 solvate thereof) is administered to achieve complete attack resolution. The term “complete attack

resolution” in this context can mean that the treatment improves the severity of the attack to “none” when assessed using the PGI-S scale.

When assessed using the PGI-S scale, in any of the treatments of the invention, sebetralstat is administered to achieve complete attack resolution within about 8 and about 24 hours. Complete attack resolution can be achieved within 24 hours. Complete attack resolution can be achieved within about 8 and about 20 hours. Complete attack resolution can be achieved within about 8 and about 17 hours. Complete attack resolution can be achieved within about 8 and about 13 hours. Complete attack resolution can be achieved within about 8 and about 10 hours.

Dosage forms that can be used in the treatments described herein

In any of the embodiments described herein, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can preferably be administered as part of a pharmaceutical composition. Sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can administered as an oral dosage form comprising: (i) sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and (ii) at least one pharmaceutically acceptable excipient. The oral dosage form can be a capsule. The oral dosage form can be a tablet. In particular, the tablet can be a film-coated tablet or an orodispersible tablet.

The oral dosage form can be a film-coated tablet comprising microcrystalline cellulose as a diluent, croscarmellose sodium as a disintegrant, polyvinyl pyrrolidone as a binder, and optionally magnesium stearate as a lubricant. In a preferred tablet, sebetralstat comprises: (i) at least about 40 wt% of the tablet (more specifically about 40 wt% to about 60 wt%), compared to the total mass of the tablet; (ii) about 25 wt% to about 60 wt% of the diluent (more specifically about 25 wt% to about 40 wt%, compared to the total mass of the tablet; (iii) about 1 wt% to about 15 wt% of the disintegrant (more specifically about 2 wt% to about 6 wt%), compared to the total mass of the tablet; (iv) about 1 wt% to about 20 wt% of the binder (more specifically about 2 wt% to about 5 wt%), compared to the total mass of the tablet; and when present, (v) about 0.1 to about 5 wt% lubricant (more specifically about 0.1 wt% to about 1.5 wt%), compared to the total mass of the tablet. The dosage form can be a tablet containing about 250mg to about 350mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The dosage form can be a tablet containing about 270mg to about 330mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The dosage form can be a tablet containing about 275mg to about 325mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The dosage form can be a tablet containing about 285mg to about 315mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The dosage form can be a tablet containing about 290mg to about 310mg of

sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). The dosage form can be a tablet containing about 295mg to about 305mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof). Preferably, the dosage form can be a tablet containing about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

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The tablet can further comprise extragranular excipients comprising: microcrystalline cellulose as an extragranular diluent, croscarmellose sodium as an extragranular disintegrant, polyvinyl pyrrolidone as an extragranular binder, and/or magnesium stearate as an extragranular lubricant.

- 10 The dosage forms described herein (e.g. the tablets) can be film coated, wherein the film coating can comprise one or more of hypromellose, lactose monohydrate, titanium dioxide and triacetin.

- In any of the embodiments described herein, sebetralstat is administered as an orodispersible tablet. The orodispersible tablet can comprise one or more of mannitol (e.g. granulated mannitol and/or spray-dried mannitol (e.g. Mannogem EZ®)) as a filler, microcrystalline cellulose (e.g. silicified microcrystalline cellulose) as a binder and polyvinylpyrrolidone (crospovidone) as a disintegrant. In particular, the orodispersible tablet can comprise between about 25 and about 50 wt% of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), one or more fillers (e.g. granulated mannitol and/or spray-dried mannitol) present at between about 30 and 80 wt% of the orodispersible tablet, one or more binders (e.g. silicified microcrystalline cellulose) present at between about 5 and about 30 wt% of the orodispersible tablet and one or more disintegrants (e.g. polyvinylpyrrolidone (crospovidone)) present at between 1 and about 10 wt% of the orodispersible tablet.

Symptoms

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- In the treatments of the invention, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can be orally administered on-demand upon recognition of a symptom of an HAE attack. In the treatments of the invention, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can be orally administered on-demand at the earliest recognition of an HAE attack. In the treatments of the invention, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can be orally administered on-demand for the treatment of patient-recognized attacks of HAE.

- Although each HAE attack can be different in severity and in terms of the area affected, patients who suffer from HAE, medical professionals with knowledge of HAE, and carers of HAE patients are (and indeed the skilled person would be) astute in identifying symptoms of an HAE attack. These symptoms include,

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but are not limited to: swelling of tissues such as in the hands, feet, limbs, face, intestinal tract, and/or airway; fatigue; headache; muscle aches; skin tingling; abdominal pain; nausea; vomiting; diarrhoea; difficulty swallowing; hoarseness; shortness of breath; and/or mood changes. Thus, in some embodiments, administration of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can occur upon recognition of at least one of the above symptoms.

The skilled person would also understand that “administered upon recognition of a symptom of a HAE attack” means that administration occurs as quickly as feasibly possible after the symptom of an HAE attack is recognised. For example, patients are expected to have sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) easily and readily available at all times (most likely in the form of a pharmaceutically acceptable composition) to ensure that treatment can occur upon recognition of a symptom of a HAE attack. In other words, the treatment occurs on-demand. For example, sebetralstat can be administered within 1 hour of the symptom of an HAE attack being recognised, preferably within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, within about 6 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.

If the symptom of an HAE attack is recognised in the prodromal phase, sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) can be administered in the prodromal phase of an HAE attack. In these circumstances, the symptom recognised can be a slight swelling, in particular, a slight swelling affecting the face and neck. In addition, or in the alternative, the symptom can be abdominal pain, in particular, abdominal pain is considered to be characteristic of a HAE attack. In addition, or in the alternative, the symptom can be a reddening of the skin such as erythema marginatum.

In any of the above treatments, the symptom can be recognised by the patient. In any of the above treatments, the symptom can be recognised by a medical professional such as a medical professional with knowledge of HAE. In any of the above treatments, the symptom can be recognised by a carer of the patient.

Figures

In the Figures, the term “Compound” means sebetralstat.

Figure 1: X-ray powder diffraction pattern of the sebetralstat as generated in Example 1.

- Figure 2: Chart showing the distribution of attack severity (PGI-S) at baseline in patients using on-demand treatment $\pm$ LTP.
- Figure 3: Chart showing the distribution of attack severity (PGI-S) at baseline in patients using sebetralstat 300mg, sebetralstat 600mg or placebo.
- 5 Figure 4: Graph showing the time from onset of attack to the first IMP administration.
- Figure 5: Graph showing the cumulative % of patients with symptom relief (PGI-C) within 12 hours of IMP administration.
- Figure 6: Graph showing the cumulative % of patients with a reduction in attack severity (PGI-S) within 12 hours of IMP administration.
- 10 Figure 7: Graph showing the cumulative % of patients with complete attack resolution (PGI-S) within 24 hours of IMP administration.
- Figure 8: Graph showing the cumulative % of patients with a 50% reduction in composite VAS score within 24 hours of IMP administration.
- Figure 9: Graph showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inhibitor itraconazole.
- 15 Figure 10: Graph showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inhibitor itraconazole.
- Figure 11: Graph showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inducer phenytoin.
- 20 Figure 12: Graph showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inducer phenytoin.
- Figure 13: Graph showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inhibitor verapamil.
- Figure 14: Graph showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inhibitor verapamil.
- 25 Figure 15: Graph showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inducer efavirenz.
- Figure 16: Graph showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inducer efavirenz.
- 30 Figure 17: Graph showing proportion of attacks reaching primary or key secondary endpoints with 1 or 2 administrations of sebetralstat.
- Figure 18: Graph showing hazard ratios of sebetralstat 600 mg compared with 300 mg for primary or key secondary endpoints by baseline attack severity.
- Figure 19: Graph showing hazard ratios of sebetralstat 600 mg compared with 300 mg for primary or key secondary endpoints by treatment paradigm.
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Figure 20: Graph showing number of sebetralstat-treated attacks in the open-label extension Phase 3 study of sebetralstat (Example 5).

Figure 21: Graph showing time from attack recognition to sebetralstat administration in the open-label extension Phase 3 study of sebetralstat (Example 5).

5 Figure 22: Graph showing time from onset of attack to treatment administration (Example 4).

Figure 23: Graph showing the probability for faster complete attack resolution (Example 4).

Figure 24: Graph showing time to complete attack resolution within 24 hours versus time to treatment for “mild”, or “moderate” or greater, attacks treated “earlier” and “later” (Example 4).

10 Figure 25: LOESS regression curve fitting time to complete attack resolution within 24 hours versus time to treatment (Example 4).

Figure 26: Graph showing baseline attack severity in attacks involving the larynx (Examples 4 and 5).

Figure 27: Graph showing time to treatment administration in all attacks treated in Example 4, all attacks treated in Example 5 and attacks involving the larynx treated in Examples 4 and 5.

15 Figure 28: Graph showing the proportion of attacks involving the larynx that reached primary and key secondary endpoints without an additional dose (Examples 4 and 5).

Figure 29: Graph showing sebetralstat effectiveness among participants receiving LTP in the open-label extension Phase 3 study of sebetralstat (Example 5).

Figure 30: Graph showing sebetralstat effectiveness among participants receiving berotralstat in the open-label extension Phase 3 study of sebetralstat (Example 5).

20 Figure 31: Graph showing effectiveness endpoints in attacks involving the larynx treated with sebetralstat in the open-label extension Phase 3 study of sebetralstat (Example 5).

Embodiments provided herein may be more fully understood by reference to the following examples. These examples are meant to be illustrative of treatments provided herein but are not in any way limiting.

25 Indeed, the scope of the invention is defined by the claims.

While examples of certain particular embodiments are provided herein, it will be apparent to those skilled in the art that various changes and modifications may be made. Such modifications are also intended to fall within the scope of the appended claims.

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General Experimental Details

In the following examples, the following abbreviations and definitions are used:

Aq	Aqueous solution
DCM	Dichloromethane

DDI	Drug-drug interaction
DMF	N,N-Dimethylformamide
EtOAc	Ethyl Acetate
FXII	Factor XII
FXIIa	Factor XIIa
HAE	Hereditary angioedema
HK	High molecular weight kininogen
Hrs	Hours
HOBt	Hydroxybenzotriazole
IMP	Investigational Medicinal Product
IPA	2-Propanol / Propan-2-ol / Iso-propanol
LCMS	Liquid chromatography mass spectrometry
LTP	Long-term prophylaxis
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Min	Minutes
MS	Mass spectrum
NMR	Nuclear magnetic resonance spectrum – NMR spectra were recorded at a frequency of 400MHz unless otherwise indicated
ODT	Orodispersible tablet
Ph	Phenyl
PKa	Plasma kallikrein
PPK	Plasma prekallikrein
Sebetralstat	N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-[(2-oxopyridin-1-yl)methyl]phenyl)methyl]pyrazole-4-carboxamide
Rt	room temperature
THF	Tetrahydrofuran
XRPD	X-ray powder diffraction

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

¹H NMR spectra were recorded on a Bruker (400MHz) or on a JEOL (400MHz) spectrometer with reference to deuterium solvent and at rt.

Molecular ions were obtained using LCMS which was carried out using a Chromolith Speedrod RP-18e column, 50 x 4.6 mm, with a linear gradient 10% to 90% 0.1% HCO₂H/MeCN into 0.1% HCO₂H/H₂O over 13 min, flow rate 1.5 mL/min, or using Agilent, X-Select, acidic, 5-95% MeCN/water over 4 min. Data was collected using a Thermofinnigan Surveyor MSQ mass spectrometer with electrospray ionisation in conjunction with a Thermofinnigan Surveyor LC system.

Alternatively, molecular ions were obtained using LCMS which was carried out using an Agilent Poroshell 120 EC-C18 (2.7µm, 3.0 x 50mm) column with 0.1% v/v Formic acid in water [eluent A]; MeCN [eluent B]; Flow rate 0.8mL/min and 1.5 minutes equilibration time between samples, gradient shown below. Mass detection was afforded with API 2000 mass spectrometer (electrospray).

Gradient:

Time (min)	Eluent A (%)	Eluent B (%)
0.00	95	5
0.20	95	5
2.00	5	95
3.00	5	95
3.25	95	5
3.50	95	5

Where products were purified by flash chromatography, 'silica' refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Merck silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Reverse phase preparative HPLC purifications were carried out using a Waters 2525 binary gradient pumping system at flow rates of typically 20 mL/min using a Waters 2996 photodiode array detector.

All solvents and commercial reagents were used as received.

Chemical names were generated using automated software such as the Autonom software provided as part of the ISIS Draw package from MDL Information Systems or the Chemaxon software provided as a component of MarvinSketch or as a component of the IDBS E-WorkBook.

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X-Ray Powder Diffraction patterns were collected on a Philips X-Pert MPD diffractometer and analysed using the following experimental conditions (Method A), unless otherwise specified:

Tube anode: Cu

Generator tension: 40 kV

Tube current: 40 mA

Wavelength alpha1: 1.5406 Å

5 Wavelength alpha2: 1.5444 Å

Start angle [2θ]: 4

End angle [2θ]: 40

Continuous scan

10 Approximately 2 mg of sample under analysis was gently compressed on the XRPD zero back ground single obliquely cut silica sample holder. The sample was then loaded into the diffractometer for analysis.

Example 1 – Preparation of sebetralstat

A. 1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one

15 4-(Chloromethyl)benzylalcohol (5.0 g, 31.93 mmol) was dissolved in acetone (150 mL). 2-hydroxypyridine (3.64 g, 38.3 mmol) and potassium carbonate (13.24 g, 95.78 mmol) were added and the reaction mixture was stirred at 50 °C for 3 hrs after which time the solvent was removed *in vacuo* and the residue taken up in chloroform (100 mL). This solution was washed with water (30 mL), brine (30 mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3% MeOH / 97%

20 CHCl₃, to give a white solid identified as 1-(4-hydroxymethyl-benzyl)-1H-pyridin-2-one (5.30g, 24.62mmol, 77% yield).

[M+Na]⁺ = 238

B. 1-(4-Chloromethyl-benzyl)-1H-pyridin-2-one

25 1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (8.45 g, 39.3 mmol), dry DCM (80 mL) and triethylamine (7.66 ml, 55.0 mmol) were cooled in an ice bath. Methanesulfonyl chloride (3.95 ml, 51.0 mmol) was added and stirred in ice bath for 15 min. The ice bath was removed and stirring continued at rt temperature overnight. The reaction mixture was partitioned between DCM (100 mL) and saturated aqueous NH₄Cl solution (100 mL). The aqueous layer was extracted with further DCM (2 x 50 mL) and the

30 combined organics washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give 1-(4-chloromethyl-benzyl)-1H-pyridin-2-one (8.65 g, 36.6 mmol, 93 % yield) as a pale yellow solid.

[MH]⁺ = 234.1

C. Methyl 3-(methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate

Potassium carbonate (519 mg, 3.76 mmol) was added to a solution of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (320 mg, 1.88 mmol; CAS no. 318496-66-1 (synthesised according to the method described in WO 2012/009009)) and 1-(4-(chloromethyl)benzyl)pyridin-2(1H)-one (527 mg, 2.26 mmol) in DMF (5 mL) and heated at 60 °C overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (2 x 100 mL), dried over magnesium sulfate, filtered and reduced *in vacuo*. The crude product was purified by flash chromatography (40 g column, 0-100% EtOAc in isohexanes) to afford two regioisomers. The second isomer off the column was collected to afford methyl 3-(methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (378 mg, 1.01 mmol, 53.7 % yield) as a colourless gum.

[MH]⁺ = 368.2

D. 3-(Methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid

To methyl 3-(methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (3.77 g, 10.26 mmol) in THF (5 mL) and MeOH (5 mL) was added 2M NaOH solution (15.39 mL, 30.8 mmol) and stirred at rt overnight. 1M HCl (50 mL) was added and extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and reduced *in vacuo* to give 3-(methoxymethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (1.22 g, 3.45 mmol, 33.6 % yield) as a white powder.

[MH]⁺ = 354.2

E. 3-Fluoro-4-methoxy-pyridine-2-carbonitrile

To a large microwave vial, copper (I) cyanide (1.304 g, 14.56 mmol) was added to a solution of 2-bromo-3-fluoro-4-methoxypyridine (1 g, 4.85 mmol) in DMF (5 mL). The reaction vial was sealed and heated to 100 °C for 16 hrs. The reaction mixture was diluted with water (20 mL) and EtOAc (20 mL). The thick suspension was sonicated and required additional water (40 mL) and EtOAc (2 x 50 mL) with sonication to break-up the solid precipitated. The combined layers were filtered through a plug of celite and the organic layer isolated, washed with brine (50 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a pale green solid identified as the desired compound 3-fluoro-4-methoxy-pyridine-2-carbonitrile (100 mg, 0.578 mmol, 12 % yield)

F. (3-Fluoro-4-methoxy-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester

3-Fluoro-4-methoxy-pyridine-2-carbonitrile (100 mg, 0.578 mmol) was dissolved in anhydrous methanol (10 mL, 247 mmol) and nickel chloride hexahydrate (14 mg, 0.058 mmol) was added followed by di-tert-butyl dicarbonate (255 mg, 1.157 mmol). The resulting pale green solution was cooled in an ice-salt bath to -5 °C and then sodium borohydride (153 mg, 4.05 mmol) was added portion wise maintaining the

reaction temperature $\sim 0^{\circ}\text{C}$. The deep brown solution was left to stir at 0°C and slowly allowed to warm to rt and then left to stir at rt for 3 hrs. The reaction mixture was evaporated to dryness at 40°C to afford a black residue which was diluted with DCM (10 mL) and washed with sodium hydrogen carbonate (10 mL). An emulsion formed so the organics were separated *via* a phase separating cartridge and concentrated. The crude liquid was purified by chromatography eluting with EtOAc / iso-Hexane to afford the title compound, (3-fluoro-4-methoxy-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester as a clear yellow oil (108 mg, 62 % yield)

[MH]⁺ = 257

10 G. C-(3-Fluoro-4-methoxy-pyridin-2-yl)-methylamine hydrochloride salt

(3-Fluoro-4-methoxy-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester (108mg, 0.358mmol) was taken up in iso-propyl alcohol (1 mL) and then HCl (6N in iso-propyl alcohol) (1 mL, 0.578 mmol) was added at rt and left to stir at 40°C for 2 hrs. The reaction mixture was concentrated under reduced pressure and then triturated with ether, sonicated and then decanted to give a cream coloured solid (75 mg, 55% yield)

15 identified as C-(3-fluoro-4-methoxy-pyridin-2-yl)-methylamine hydrochloride salt.

[MH]⁺ = 157

Example 1a - N-[(3-Fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-[(4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl]pyrazole-4-carboxamide (sebetralstat)

20 3-(Methoxymethyl)-1-(4-[(2-oxopyridin-1(2H)-yl)methyl]benzyl)-1H-pyrazole-4-carboxylic acid (825 mg, 2.34 mmol) and C-(3-fluoro-4-methoxy-pyridin-2-yl)-methylamine hydrochloride salt (450 mg, 2.34 mmol) were dissolved in DCM while cooling to 0°C . 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (627.0 mg, 3.27 mmol), HOBT (378.8 mg, 2.80 mmol) and triethylamine (1.63 mL, 1182 mmol) were added while stirring, the mixture allowed to warm to rt and stirring continued for 20 hrs.

25 Chloroform (50 mL) was added, the mixture was washed with saturated $\text{NaHCO}_3(\text{aq})$ and reduced *in vacuo*. The crude material was purified by chromatography eluting with methanol/DCM. The solvent was removed *in vacuo* and the resulting solid triturated with diethyl ether. The resulting solids were collected by filtration to afford the sebetralstat.

[MH]⁺ = 492.0

30 NMR (CD_3OD) δ : 3.41 (3H, s), 4.03 (3H, s), 4.65 (2H, s), 4.72 (2H, d, J=2.3Hz), 5.24 (2H, s), 5.37 (2H, s), 6.44 (1H, td, J = 1.4, 6.8Hz), 6.62 (1H, d, J = 9.0Hz), 7.18-7.22 (1H, m), 7.31-7.38 (4H, m), 7.56-7.60 (1H, m), 7.75 (1H, dd, J = 1.9, 7.1Hz), 8.18 (1H, s), 8.27 (1H, d, J = 5.6Hz) ppm.

An XRPD diffractogram of sebetralstat resultant from the above procedure is shown in Figure 1.

Peak position table:

No.	Pos. [°2Th.]	Rel. Int. [%]
1	4.436	32.36
2	5.0471	58.74
3	10.2255	43.07
4	11.2061	48.44
5	12.0101	16.4
6	12.5494	37.17
7	13.165	67.26
8	14.4984	38.94
9	15.8919	23.54
10	16.2983	34.56
11	17.4492	36.63
12	17.8564	71.49
13	18.6888	21.9
14	20.285	26.12
15	21.1598	100
16	22.04	87.76
17	22.5857	36.38
18	23.4408	14.33
19	24.3045	31.11
20	25.1655	78.97
21	25.3728	93.91
22	26.4946	56.79
23	27.991	76.91
24	28.7495	22.99
25	30.7611	13.4
26	32.413	17.2
27	37.2144	14.13
28	38.1171	14.14

Example 2 – Preparation of a dosage form comprising sebetralstat

Blending and Roller Compaction

- 5 Equipment: Freund Vector TFC Lab Micro Roller Compactor and Granulator (*the roller compactor and granulator are separate entities*). The equipment parameters are below:

Parameter	Range Used
Screw Speed (rpm)	10.0 – 20.0
Roll Speed (rpm)	1.0 – 2.0
Roll Force (kN)	0.50 – 12.00
Granulator Screen Size (mm)	1

Method

10

Three tablet formulations (Tablets A, B and C) were prepared according to the following method at 30g blend scale to produce tablets having components in the amounts shown below.

	Component	wt% (compared to the total mass of the tablet)		
		Tablet A	Tablet B	Tablets C and D
Intragranular	Sebetralstat	42.5	47.5	55.9
	Microcrystalline Cellulose (Avicel PH101)	34.5	29.5	34.9
	Croscarmellose Sodium (Ac-di-sol)	4	4	4.7
	Polyvinyl Pyrrolidone (Kollidon 30)	3	3	3.5
Extragranular	Microcrystalline Cellulose (Avicel PH102)	15	15	0
	Magnesium Stearate	1	1	1

For each of the tablets, blends were prepared by passing the intragranular components through a 355 µm sieve at a suitable scale for the scope of the roller compactor in a glass vessel using a Turbula Blender at 34 rpm. The blend was then run through the roller compactor using the parameters described above. The ribbons produced were collected into a suitably sized container. The collected ribbons were then subjected to the granulator fixed with a 1 mm screen and the resultant granules were collected for further downstream processing.

Tabletting

Equipment: RIVA Mini single station Tablet Press (Tablets A and B). Rotary Press (Tablets C and D) run at 5 rpm.

The equipment parameters are shown below:

Parameter	Range Used (for Tablets A and B, both 100mg)	Approx. Value Used (for Tablet C, 300mg Round)	Approx. Value Used (for Tablet D, 300mg Oval)
Tooling Diameter	8 mm round	12 mm round	15.5 mm x 9.0 mm oval
Force (kN)	6 - 10	17.5	17.5
Fill Weight (mg)	178 - 300	537	537

The granules were subsequently blended with their extragranular excipients, respectively. The extragranular excipients were prepared by screening through a 355 µm sieve in a glass vessel using a Turbula Blender at 34 rpm. The target tablet weight was then dispensed and compressed into tablets. Tablet A was compressed at 7.2 to 8.8 kN compression force. Tablet B was compressed at 6.9 to 7.7 kN compression force. Tablets C and D were compressed at approximately 17.5 kN compression force.

The tablets were found to be robust. Tablets A, B, C and D were subsequently submitted for long-term stability testing.

The production of tablets A and B per the method described above has been scaled to 180g with a roller compaction time of approximately 60 minutes. Tablets C and D were scaled to 9.66kg. Tablets C and D were film-coated with Opadry® II White (85F280012) (4% w/w).

Example 3 – Preparation of an orodispersible tablet comprising sebetralstat

ODTs of sebetralstat were prepared according to the following method.

5 **Method**

1. Add sebetralstat, silicified microcrystalline cellulose, crospovidone, sucralose NF, silicon dioxide, peppermint natural flavour to the blender and blend to form a powder mixture.
2. Add granulated mannitol, spray-dried mannitol (e.g. Mannogem EZ®) to the powder mixture from
10 step 1 in the blender and blend.
3. Compress the final blend with external magnesium stearate as lubricant into tablets.

Table 1: Composition of sebetralstat 250 mg and 300 mg Orodispersible Tablets (ODTs)

Components	Function/ Standard	Blend composition	Sebetralstat 250 mg ODT	Sebetralstat 300 mg ODT
		% w/w	mg	mg
Sebetralstat	Active	30.0	250.0	300 .0
Mannitol (Granulated)	Diluent (USP/NF, Ph Eur, JP)	26.85	223.7	268.5
Mannitol (Mannogem EZ)	Diluent (USP/NF, Ph Eur, JP)	26.85	223.7	268.5
Silicified Microcrystalline Cellulose	Diluent (USP/NF, Ph Eur, JP)	10.00	83.3	100.0
Crospovidone	Disintegrant (USP/NF, Ph Eur, JP)	5.00	41.7	50.0
Sucralose	Sweetener (USP/NF, Ph Eur)	0.50	4.2	5.0
Silicon Dioxide	Flow Enhancer (USP/NF, Ph Eur, JP)	0.75	6.3	7.5
Peppermint Natural Flavour	Flavour	0.05	0.4	0.5
Total*	-----	100.00	833.3	1,000

*Trace of Magnesium Stearate (USP/NF, Ph Eur, JP) for external lubrication only

The orodispersible tablets according to Table 1 have been made on a 5 kg scale.

Example 4 – Phase 3 study of sebetralstat

5 A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of sebetralstat (“the compound” or “study drug”), an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II.

10 Clinicaltrials.gov identifier: NCT05259917.

Objectives:

Primary Objective:

- 15 • To demonstrate the clinical efficacy of the compound compared with placebo for the on-demand treatment of HAE attacks.

Secondary Objective:

- 20 • To investigate the safety and tolerability of the compound.

Setup:

25 This was a double-blind, randomized, placebo-controlled, multicentre clinical trial in patients 12 years or older with HAE type I or II. Patients were randomized to 6 treatment sequences in a 3-way crossover design. Eligible attacks were initially treated with a single dose of placebo, 300 mg, or 600 mg of the compound (sebetralstat) per attack with a minimum 48-hour washout period between each eligible attack and last dose of compound or conventional on-demand treatment. If needed (as determined by the patient), a second dose of the study drug was administered for each attack.

30

The estimated duration of this trial for each randomized patient was approximately 25 weeks from screening through the final visit and includes the treatment of 3 eligible attacks during the treatment period.

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

10 ***Screening Visit***

Eligible patients ≥ 12 years old underwent a screening assessment for trial inclusion. All patients provided informed consent or assent prior to any trial-related procedures being performed. Informed consent and assent may have been collected through e-consent if allowed through country and site regulations.

15

During the visit, a physical exam, 12-lead electrocardiogram (ECG), laboratory tests (including diagnostic testing for HAE), and other assessments was performed.

Site personnel trained patients on the information they will be expected to provide in the electronic diary (eDiary) and the use of the study drug.

20

Randomization Visit

Within 4 weeks of the Screening Visit, patients participated in a Randomization Visit. Patients were assigned to receive 3 treatments in randomized, double-dummy blinded, crossover fashion based on their assignment to 1 of 6 treatment sequences. Randomization was stratified by whether the patient enters the trial taking only conventional on-demand treatment vs. on a stable dose and regimen of long-term prophylactic treatment. Randomization occurred in a 1:1:1:1:1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment sequence. Each patient received the following treatments:

30

- 300 mg of the compound, sebetralstat (1 x 300 mg tablet plus 1 matching placebo tablet)
- 600 mg of the compound, sebetralstat (2 x 300 mg tablets)
- 2 matching placebo tablets

35

Patients treated each eligible attack with up to 2 doses of the study drug, administered at least 3 hours apart. The second dose, if taken, was the same assigned treatment as the first dose.

5 In this trial, the study drug was shipped directly to the patients via a courier service or was dispensed at the trial clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual.

Treatment of Eligible HAE Attacks

10 Patients treated 3 separate, eligible HAE attacks with their assigned study drug treatment for that attack. For an HAE attack to be considered eligible for treatment with the study drug, the attack must have met the following criteria:

- The attack was not a severe laryngeal attack.
- 15 • Patient must have been able to identify the start time of the attack.
- At least 48 hours must have elapsed since patient has used conventional on-demand treatment or the study drug to treat an HAE attack.
- Patient must have been able to complete at least the first 4 hours of eDiary assessments following the first administration of the study drug.
- 20 • Post-attack televisit must have been completed for the previous eligible attack (applicable to eligible attacks 2 and 3 only).

Eligible attacks should initially have been treated with a single administration of the study drug. Patients were encouraged to treat as soon as possible after the start of the attack.

25

If needed (as determined by the patient), a second dose of the study drug was administered for each attack, as follows:

Non-laryngeal attacks

- 30 For each eligible HAE attack, a second dose of the study drug may have been taken:
- after 3 hours if HAE attack symptoms were considered severe enough by the patient to require a second dose of the study drug.

After the second dose of the study drug, conventional on-demand treatment may have been taken:

- after 1 hour if HAE attack symptoms were considered severe enough by the patient to require treatment with conventional treatment.

If symptoms progressed to airway involvement, patients may have treated with conventional on-demand
5 treatment at any time.

Laryngeal attacks

After the first dose of the study drug, conventional on-demand treatment may have been taken at any time:

- if HAE attack symptoms worsened or if HAE attack symptoms were considered severe enough by the patient to require immediate treatment.

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

15

Conventional on-demand treatments may have included plasma derived C1-inhibitor (pdC1-INH) intravenous (iv), recombinant human C1-esterase inhibitor (rC1-INH) iv, icatibant sc, or ecallantide sc.

Patients with safety or tolerability concerns contacted the Investigator or designee as soon as possible or
20 the nearest emergency service as appropriate.

Study Call Center

After the first dose of the study drug and prior to the second dose or conventional on-demand treatment,
25 patients were required to call a designated Study Call Center to be reminded of the repeat dosing criteria.

Patients contacted the Call Center:

1. After the first dose of the study drug
2. Prior to a second dose of the study drug
- 30 3. Prior to a dose of conventional on-demand treatment.

The Call Center staff reminded patients of the rules for re-dosing and the eDiary assessment requirements. The Call Center did not collect any data during the call.

Patient eDiary

For each HAE attack treated with the study drug, patients recorded information in an eDiary, including attack location, attack symptoms, date/time of onset, attack severity, time of second study drug dose, if applicable, and use of conventional on-demand treatment, if applicable. Patients completed timed assessments of their HAE attack through 48 hours as documented in Table 2. Patients should have completed all timed diary assessments except during sleep; however, patients must have completed at least the first 4 hours of diary assessments following the first administration of the study drug.

Table 2: Frequency of Patient Assessment

Time Period following Study Drug Administration	Frequency of Patient Assessment*	Allowed Time Window for Assessment
0 to 4 hours	Every 0.5 hours	± 0.25 hour
5 to 12 hours	Every 1 hour	± 0.5 hour
14 to 24 hours	Every 2 hours	± 1 hour
25 to 48 hours	Every 12 hours	± 3 hours

** If a second dose of IMP or additional doses of conventional on-demand treatment were needed, patients completed diary assessments prior to taking each additional dose. After re-dosing, the planned post-dose diary assessments continued through 48 hours after first dose of the study drug.*

Post-Attack Televisit

A televisit (between the site staff and the patient) was completed following each administration of the study drug to ensure the safety and wellbeing of the patient, to confirm the study drug accountability, to review the patient diary (and retrain, if necessary), and to undergo an adverse event (AE) and concomitant medication review. The televisit occurred by the next working day after the completion of the patient diary (visit window: +1 week).

Final Visit/Early Termination

Once 3 HAE attacks were treated, or upon early termination, the patient returned to the clinic as soon as possible within 1 week for an in-clinic visit to undergo final safety checks including AE reporting, vital sign

recording, and blood sampling for laboratory safety measurements. Whenever possible, this visit should have been completed prior to starting any new medication or treatment.

Investigational Medicinal Product:

5

Sebetralstat – 300 mg film-coated tablet. These contained the following excipients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate; the aesthetic coating contains polyvinyl alcohol, titanium dioxide and polyethylene glycol 3350.

10 Placebo for the compound tablet. These contained microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate and are film-coated; the aesthetic coating contains polyvinyl alcohol, titanium dioxide and polyethylene glycol 3350.

No study drug dose modifications were allowed in this study.

15

Tablets must have been swallowed whole and were not to be crushed or modified in any way. Eligible attacks should initially have been treated with a single administration of the study drug as soon as possible after the start of the attack. If needed (as determined by the patient), a second dose of the study drug may have been administered for each attack.

20

Number of Patients:

The trial population comprised 2 subsets: (1) patients who entered the trial taking only conventional on-demand treatment and (2) patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

25

Population:

The trial population included male and female patients 12 years of age and older with a confirmed diagnosis of HAE type I or II.

30

The trial population included a subset of patients who enter the trial taking only conventional on demand treatment and a subset of patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

35

Inclusion Criteria:

1. Male or female patients 12 years of age and older.
2. Confirmed diagnosis of HAE type I or II at any time in the medical history:
 - a. Documented clinical history consistent with HAE (sc or mucosal, nonpruritic swelling episodes without accompanying urticaria) and either:
 - i. Diagnostic testing results obtained during the Screening Period that confirm HAE type I or II: C1-INH functional level <40% of the normal level. Patients with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Patients may be retested during the Screening Period if results are incongruent with clinical history or believed by the Investigator to be confounded by recent prophylactic or therapeutic C1-INH use, or
 - ii. Documented genetic results that confirm known mutations for HAE type I or II.
3. Patient has access to and ability to use conventional on-demand treatment for HAE attacks.
4. If a patient is receiving long-term prophylactic treatment with one of these medicines indicated for HAE: intravenous (iv) or sc plasma-derived C1-INH, and/or lanadelumab, they must be on a stable dose and regimen for at least 3 months prior to the Screening Visit and be willing to remain on a stable dose and regimen for the duration of the trial.
5. Patient's last dose of attenuated androgens was at least 28 days prior to randomization.
6. Patient has had at least 2 documented HAE attacks within 3 months prior to randomization.
7. Patients must meet one of the following contraception requirements as follows:
 - a. Female patients who are fertile and heterosexually active must agree to use contraception from the Screening Visit until the Final or Early Termination (ET) Visit. Acceptable methods of contraception include one or more of the following:
 - i. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable (hormonal contraception that contains estrogen including ethinylestradiol is excluded per Exclusion 4).
 - ii. Intrauterine device.
 - iii. Intrauterine hormone-releasing system.
 - iv. Bilateral tubal occlusion.
 - v. Vasectomized partner (provided that the partner is the sole heterosexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of surgical success).
 - vi. Male or female condom.
 - vii. Cap, diaphragm, or sponge with spermicide.

- b. Patients who are not fertile or not heterosexually active, as defined below, do not require contraception. If the patient's status changes during the course of the trial, they will be required to meet the requirements specified in Inclusion Criterion 7a.
- i. Female patients who refrain from heterosexual intercourse during the trial if the reliability of the heterosexual abstinence has been evaluated in relation to the duration of the clinical trial and is the preferred and usual lifestyle of the patient.
- ii. Female patients who are surgically sterile (e.g. status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
- iii. Female patients who are premenarche and remain premenarcheal until the end of the trial.
- iv. Male patients (including female partners).
8. Patients must be able to swallow trial tablets whole.
9. Patients, as assessed by the Investigator, must be able to appropriately receive and store the study drug, and be able to read, understand, and complete the electronic diary (eDiary).
10. Investigator believes that the patient is willing and able to adhere to all protocol requirements.
11. Patient provides signed informed consent or assent (when applicable). A parent or legally authorized representative must also provide signed informed consent when required.

Exclusion criteria:

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria.
2. A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator.
3. Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization.
4. Any estrogen containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit.
5. Use of strong cytochrome P450 3A4 CYP3A4 inhibitors and inducers during participation in the trial, starting within 5 half-lives of the Screening Visit.
- Note: These medications include but are not limited to the following:
- Inhibitors:** boceprevir, clarithromycin, cobicistat, dasabuvir, denoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole.
- Inducers:** apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort.
6. Inadequate organ function, including but not limited to:

- a. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
 - b. Aspartate aminotransferase (AST) >2x ULN
 - c. Bilirubin direct >1.25x ULN
 - d. International normalized ratio (INR) >1.2
- 5 e. Clinically significant hepatic impairment defined as a Child-Pugh B or C.
7. Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial.
8. History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator.
- 10 9. Known hypersensitivity to the compound or placebo or to any of the excipients.
10. Prior participation in the phase 2 trial.
11. Participation in any gene therapy treatment or trial for HAE.
12. Participation in any interventional investigational clinical trial, including an investigational COVID 19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to screening.
- 15 13. Any pregnant or breastfeeding patient.

Assessments:

Efficacy Variables:

- 20 • Patient global impression of change (PGI-C) scored on a 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse.
- Patient global impression of severity (PGI-S) scored on a 5-point rating scale as none, mild, moderate, severe, and very severe.
- Visual analog scale (VAS) anchored at 0 (none) and 100 (very severe) for abdominal pain, skin pain, and skin swelling.
- 25 • Modified General Anxiety – Numeric Rating Scale (GA-NRS) scored on an 11-point scale anchored at 0 (not at all anxious) and 10 (extremely anxious).
- Use of conventional on-demand treatment.

30 *Safety Variables:*

- Adverse events, including serious adverse events.
- Laboratory test results.
- 12-lead ECG.
- Vital signs.

- Physical examination findings.

Criteria for Evaluation of Efficacy

5 *Primary Efficacy Endpoints:*

- PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first study drug administration.

Key Secondary Efficacy Endpoints:

- 10
- PGI-S: Time to first incidence of decrease from baseline within 12 hours of the first study drug administration.
 - PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first study drug administration.

15 *Secondary Efficacy Endpoints:*

- PGI-C: Proportion of attacks with beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 4 hours and within 12 hours of the first study drug administration.
 - PGI-C: Time to at least “better” within 12 hours of the first study drug administration.
 - PGI-S: Time to first incidence of decrease from baseline within 24 hours of the first study drug administration.
- 20
- Composite VAS: Time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of the first study drug administration.

Exploratory Endpoints:

- 25
- GA-NRS: Cumulative GA-NRS expressed as area under the curve over 12 and 24 hours of the first study drug administration.

Safety

- 30
- Safety analyses were performed by treatment group using the safety set. Safety endpoints included AE, clinical laboratory assessments, vital signs, and ECG findings.

Adverse events and serious adverse events (SAEs) recorded during the trial were summarized by system organ class, preferred term, and treatment. Adverse events and medical history were coded using the most current version of MedDRA.

- 5 Frequencies and percentages of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation were provided by treatment group.

Patient listings of all AEs were provided as well as listings of deaths, SAEs, and AEs leading to discontinuation.

10

For physical examination, ECG, vital signs, and laboratory variables (measured by the central laboratory), the number and percentage of patients with normal or abnormal results were presented at each scheduled visit by sequence. Descriptive statistics for continuous variables were provided at scheduled visits together with a summary of changes from baseline for each parameter by sequence.

15

Results

Summary of the baseline characteristics of randomized patients

20

Table 3: Demographics

	Participants who treated an attack with Sebetralstat 300 mg (n = 87)	Participants who treated an attack with Sebetralstat 600 mg (n = 93)	Participants who treated an attack with Placebo (n = 84)	Total (N=110)
Age (years)				
Mean (SD)				37.7 (15.0)
Median (Q1, Q3)	37.0 (25.0, 49.0)	39.0 (25.0, 49.0)	38.0 (25.0, 49.0)	39.5 (25.0, 49.0)

Minimum, maximum				13, 74
Age (category), n (%)				
12-17				13 (11.8)
18+				97 (88.2)
Sex, n (%)				
Male	33 (37.9)	37 (39.8)	29 (34.5)	44 (40.0)
Female	54 (62.1)	56 (60.2)	55 (65.5)	66 (60.0)
BMI (kg/m ²)				
Mean (SD)				27.4 (6.3)
Median (Q1, Q3)	26.3 (22.8- 31.2)	26.2 (22.9- 30.9)	26.2 (22.9-30.8)	26.2 (22.9, 31.7)
Minimum, maximum				18.2, 45.6
Race, n (%)				
White	73 (83.9)	80 (86.0)	73 (86.9)	92 (83.6)
Black or African American	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.9)
Asian	9 (10.3)	8 (8.6)	7 (8.3)	10 (9.1)
Other	0 (0.0)	1 (1.1)	1 (1.2)	1 (0.9)
Not reported	4 (4.6)	4 (4.3)	3 (3.6)	6 (5.5)
Geography, n (%)				
US	27 (31.0)	28 (30.1)	23 (27.4)	34 (30.9)
Europe	44 (50.6)	49 (52.7)	48 (57.1)	58 (52.7)
Asia/Pacific ^a	16 (18.4)	16 (17.2)	13 (15.4)	18 (16.4)

BMI, Body mass index; Q1, 25th percentile; Q3, 75th percentile.

^a Asia/Pacific includes Australia, Israel, Japan.

Table 4: Disease-Specific Demographics

	Total (N=110)
HAE type, n (%)	
Type I	101 (91.8)
Type II	9 (8.2)
Time since HAE diagnosis (years)	
Mean (SD)	14.9 (10.3)
Median (Q1, Q3)	12.0 (7.0, 22.0)

5

Table 5: Current treatment regimen

	Total (N=110)
Current treatment regimen n (%)	
On-demand with LTP	24 (21.8)
Lanadelumab	8
Berotralstat	11
On-demand only	86 (78.2)

Summary of the baseline characteristics of the treated attacks

Figure 2 shows the distribution of attack severity (PGI-S) at baseline in patients using on-demand treatment ± long-term prophylaxis (LTP). Figure 3 shows the distribution of attack severity (PGI-S) at baseline in patients using sebetralstat 300mg, sebetralstat 600mg or placebo. Figures 2 and 3 demonstrate that patients receiving prophylactic treatment still suffer from HAE attacks and, notably, still suffer from severe and very severe HAE attacks.

15

Table 6: Summary of the Baseline Severity of the Treated HAE Attacks

	Sebetralstat 300 mg (n=85 attacks ^a)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)	Total (N=262 attacks)	On- demand (n=206 attacks)	On- demand with LTP (n=58 attacks)
Baseline PGI-S category, n (%)						
None	0	0	2 (2.4)	2 (0.8)	2 (1.0)	0
Mild	36 (42.4)	41 (44.1)	36 (42.9)	113 (43.1)	86 (41.7)	27 (46.6)
Moderate	35 (41.2)	34 (36.6)	33 (39.3)	102 (38.9)	80 (38.8)	22 (37.9)
Severe	12 (14.1)	16 (17.2)	10 (11.9)	38 (14.5)	31 (15.0)	7 (12.1)
Very severe	2 (2.4)	2 (2.2)	3 (3.6)	7 (2.7)	6 (2.9)	1 (1.7)
Baseline PGI-S score*, † — median (IQR)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)		

PGI-S, Patient Global Impression of Severity.

^a Baseline severity for 2 attacks not reported.

† Baseline PGI-S score is missing for two attacks in the sebetralstat 300-mg group.

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Figure 4 shows the time from onset of attack to the first IMP administration. The median time from onset of attack to the first IMP administration was 41.0 minutes.

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Table 7: Summary of the Baseline Characteristics of the IMP-Treated HAE Attacks

	Sebetralstat 300 mg (n=87 attacks^a)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)	Total (N=264 attacks)
Time from onset of attack to the first IMP administration (minutes), median (Q1, Q3)	35.0 (6.0, 130.0)	41.0 (5.0, 142.0)	51.0 (6.0, 166.0)	41.0 (6.0, 140.0)
Time from onset of attack to the first IMP administration category, n (%)				
≤30 minutes	42 (48.3)	41 (44.1)	36 (42.9)	119 (45.2)
>30-60 minutes	11 (12.6)	9 (9.7)	8 (9.5)	28 (10.6)
>60 minutes	33 (37.9)	43 (46.2)	40 (47.6)	116 (44.1)
Missing	1 (1.1)	0 (0)	0 (0)	1 (0.4)
Baseline primary pooled attack locations, n (%) ^b				
Neck and Above	11 (12.6)	12 (12.4)	13 (15.5)	36 (13.6)
Laryngeal	2 (2.3)	2 (2.1)	4 (4.8)	8 (3.0)
Any Abdominal	34 (39.1)	42 (43.3)	36 (42.9)	112 (42.4)
Any Subcutaneous	59 (67.8)	59 (63.4)	51 (60.7)	169 (64.0)
Missing	2 (2.3)	0 (0)	0 (0)	2 (0.8)
Baseline primary attack locations, n (%) ^c				
Abdomen	35 (40.2)	42 (45.2)	37 (44.0)	114 (43.2)
Arms/Hands	29 (33.3)	26 (28.0)	21 (25.0)	76 (28.8)
Legs/Feet	22 (25.3)	23 (24.7)	17 (20.2)	62 (23.5)
Head/Face/Neck	9 (10.3)	11 (11.8)	9 (10.7)	29 (11.0)
Torso	5 (5.7)	5 (5.4)	5 (6.0)	15 (5.7)
Genitals	2 (2.3)	4 (4.3)	3 (3.6)	9 (3.4)
Larynx/Throat	2 (2.3)	2 (2.2)	4 (4.8)	8 (3.0)
Missing	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.8)

^a 86 attacks contributed to the median. ^b Laryngeal, any laryngeal involvement including Larynx/Throat; Abdominal only; Subcutaneous only: Arms/Hands, Genitals, Legs/Feet, Head/Face/Neck, or Torso location(s) only; Abdominal and Subcutaneous: at least one abdominal location and one subcutaneous location. ^cOne attack may be reported in more than one attack location.

The median time from attack onset to treatment administration was 41 min (Q1, 6; Q3, 140), with 55.7% of participants treating in less than 1 hour. 42.8% of attacks were treated when still mild.

Table 8: Summary of the Baseline Characteristics of the IMP-Treated HAE Attacks

	Sebetralstat 300 mg (N=85)	Sebetralstat 600 mg (N=92)	Placebo (N=84)	Total (N=261)
Baseline composite VAS score				
Mean ± SD	28.6 (20.19)	29.8 (21.78)	29.7 (21.79)	29.4 (21.21)
Median (Q1, Q3)	23.3 (15.0, 40.7)	25.0 (13.3, 41.8)	22.7 (14.5, 38.0)	23.3 (13.7, 40.7)

Efficacy results

Both doses of sebetralstat (300mg and 600mg) met all primary and key secondary endpoints and demonstrated a favourable safety profile.

>90% of attacks that reached the primary endpoint did so without a second dose or before a second dose was administered.

The following data report that treatment with sebetralstat reduces the time to beginning of symptom relief, reduces the time to a reduction in attack severity and achieves complete attack resolution. These results are statistically significant.

These data also report that sebetralstat treatment can be used across a wide range of attack locations and severities, including severe attacks, and including attacks of the neck and above.

These data report that sebetralstat is effective in patients who are also being treated with a prophylactic HAE treatment (even when the prophylactic treatment is also a plasma kallikrein inhibitor), even if the HAE attack is severe.

Primary Endpoint

HAE attacks treated with both 300mg and 600mg of seabetralstat achieved the primary endpoint. The time to beginning to symptom relief was significantly faster for both 300mg ($p<0.0001$) and 600mg ($p=0.0013$) compared to placebo. The median time to beginning of symptom relief was 1.61 hours with seabetralstat 300mg, 1.79 hours with seabetralstat 600mg and 6.72 hours with placebo.

Figure 5 is a graph showing the cumulative % of patients with symptom relief (PGI-C) within 12 hours of IMP administration. Figure 5 demonstrates that the time to beginning of symptom relief was faster for both 300mg and 600mg seabetralstat compared to placebo.

Table 9: Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to Beginning of Symptom Relief Within 12 hours

	Sebetralstat 300 mg (n=87 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)
Time to beginning of symptom relief ^a (hours) n (%)	66 (75.9)	71 (76.3)	41 (48.8)
Q1 (95% CI)	0.78 (0.77, 0.98)	1.02 (0.78, 1.30)	1.34 (0.85, 2.07)
Median (95% CI)	1.61 (1.28, 2.27)	1.79 (1.33, 2.27)	6.72 (2.33, NE)
Q3 (95% CI)	7.04 (2.28, NE)	3.79 (2.78, NE)	NE (NE, NE)
Nominal <i>P</i> -value (active vs. placebo)	<0.0001	0.0006	
Adjusted <i>P</i> -value (active vs. placebo)	<0.0001	0.0013	

^aDefined as a PGI-C rating of at least "A Little Better" ≥2 time points in a row. PGI-C, Patient Global Impression of Change

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Table 10: Subgroups by Population Characteristics (time to beginning of symptom relief)

Time to beginning of symptom relief^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	n	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)
Current HAE Treatment						
On-demand with LTP	19	1.85 (0.79, 3.47)	21	2.03 (0.78, 3.41)	18	4.71 (2.28, 8.30)
On-demand	68	1.35 (0.98, 1.83)	72	1.77 (1.31, 2.27)	66	NE (2.04, NE)

Age						
Adolescent	10	2.27 (0.28, 9.36)	11	2.16 (0.33, 9.53)	9	5.54 (0.56, NE)
Adult	77	1.35 (1.03, 1.85)	82	1.77 (1.31, 2.27)	75	7.22 (2.33, NE)
Geography						
US	27	1.28 (0.78, 2.78)	28	1.77 (1.31, 2.27)	23	6.23 (2.28, NE)
Europe	44	1.78 (1.28, 3.60)	49	1.77 (1.30, 2.46)	48	5.54 (1.85, NE)
Asia/Pacific	16	1.70 (0.34, 2.27)	16	2.30 (0.79, 4.05)	13	7.76 (0.77, NE)
Category	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Diagnosis						
HAE Type 1	79	1.70 (0.79-6.54)	87	1.77 (0.98-3.40)	79	5.90 (1.33-NE)
HAE Type 2	8	1.28 (0.78-NE)	6	2.80 (1.49-NE)	5	NE (NE-NE)
Sex						
Female	54	1.78 (0.81-10.12)	56	1.77 (1.02-3.33)	55	5.57 (1.55-NE)
Male	33	1.28 (0.77-3.24)	37	1.83 (0.95->12)	29	NE (1.30-NE)

^aDefined as a PGI-C of "A Little Better" for ≥ 2 time points in a row within 12 hours of first study drug administration

Table 11: Subgroups by Attack Characteristics (time to beginning of symptom relief)

Time to beginning of symptom relief ^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)
Attack Location						
Laryngeal	2	NE (NE, NE)	2	10.97 (NE, NE)	4	5.57 (0.28, NE)
Neck and Above	11	2.78 (0.34, NE)	12	1.51 (0.28, 2.03)	13	3.67 (0.33, NE)

Abdominal only	24	0.79 (0.77, 5.21)	32	1.49 (0.79, 2.78)	29	NE (1.85, NE)
Subcutaneous only	49	1.65 (1.28, 2.27)	49	2.12 (1.68, 3.28)	44	7.27 (2.28, NE)
Abdominal and subcutaneous	10	2.23 (0.30, NE)	10	1.11 (0.28, 1.77)	7	0.81 (0.56, NE)
Mucosal (abdomen or larynx/throat)	36	1.29	44	1.32	40	5.90
Severity (controlled for baseline)						
Mild	36	1.70 (0.84, 2.28)	41	1.82 (1.30, 2.78)	36	7.22 (2.59, NE)
Moderate	35	1.56 (0.85, 3.60)	34	2.11 (1.31, 2.79)	33	2.07 (1.32, NE)
Severe	12	1.61 (0.31, NE)	16	1.70 (0.80, 2.98)	10	NE (0.28, NE)
Time to treatment						
≤Median (41 min)	46	1.80 (0.85, 5.21)	47	2.23 (1.33, 3.33)	39	4.69 (2.04, NE)
>Median	40	1.29 (0.91, 1.79)	46	1.43 (1.29, 1.99)	45	7.27 (1.85, NE)
Number of administrations						
1 administration	53	1.30 (0.81, 1.77)	56	1.38 (1.02, 1.81)	37	2.30 (1.30, 6.23)

2 administrations	34	2.36 (1.29, 7.55)	37	2.97 (1.83, 9.53)	47	NE (3.60, NE)
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*Defined as a PGI-C of "A Little Better" for ≥ 2 time points in a row within 12 hours of first study drug administration

Table 11 shows that, among severe attacks, the median time to beginning of symptom relief was 1.61 hours for 300mg sebetralstat, 1.70 hours for 600mg sebetralstat and >12 hours for placebo.

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Figure 17 is a graph showing the proportion of attacks reaching beginning of symptom relief (PGI-C) with 1 or 2 administrations of sebetralstat.

Table 11A: Proportion of Attacks Reaching Beginning of Symptom Relief (PGI-C) With 1 vs 2 Doses

Number of attacks reaching beginning of symptom relief within 12 hours, n (%)	Sebetralstat 300 mg (n = 66, 75.9%)*	Sebetralstat 600 mg (n = 71, 76.3%)*
Reached without second dose	62 (93.9)	68 (95.8)
Reached after second dose	4 (6.1)	3 (4.2)

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*Proportion of attacks reaching end point within 12 hours

The proportions of attacks that reached the beginning of symptom relief without a second dose were 93.9% and 95.8% with sebetralstat 300mg and 600mg, respectively.

15 Key Secondary Endpoints

HAE attacks treated with both 300mg ($p=0.0036$) and 600mg ($p=0.0032$) of sebetralstat achieved a significantly faster time to a reduction in attack severity from baseline compared to placebo. The median time to reduction in attack severity was 9.27 hours with sebetralstat 300mg, 7.75 hours with sebetralstat 600mg and >12 hours for placebo.

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Figure 6 is a graph showing the cumulative % of patients with a reduction in attack severity (PGI-S) within 12 hours of IMP administration. Figure 6 shows that the time to reduction in attack severity was faster for both 300mg and 600mg sebetralstat compared to placebo.

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HAE attacks treated with both 300mg ($p=0.0022$) and 600mg ($p<0.0001$) of sebetralstat demonstrated a significantly faster time to complete attack resolution compared to placebo. The median time to complete

attack resolution was >12 hours with sebetralstat 300mg, 12 hours with sebetralstat 600mg and >12 hours for placebo.

The proportion achieving complete attack resolution within 24 hours was 44.0% for 300mg sebetralstat,
5 51.7% for 600mg sebetralstat and 28.4% for placebo.

Figure 7 is a graph showing the cumulative % of patients with complete attack resolution (PGI-S) within 24 hours of IMP administration. Figure 7 shows that the time to complete attack resolution was faster for both 300mg and 600mg sebetralstat compared to placebo.

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Table 12: Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to First Incidence of Decrease Within 12 hours

	Sebetralstat 300 mg (n=87 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)
Time to first incidence of decrease in attack severity (hours) ^a n (%)	44 (50.6)	49 (52.7)	26 (31.0)
Q1 (95% CI)	1.53 (0.85, 2.78)	2.19 (1.30, 2.79)	6.23 (1.76, NE)
Median (95% CI)	9.27 (4.08, NE)	7.75 (3.27, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Nominal <i>P</i> -value (active vs. placebo)	0.0018	0.0016	
Adjusted <i>P</i> -value (active vs. placebo)	0.0036	0.0032	

^aDefined as ≥1 level decrease on PGI-S ≥2 time points in a row

15 Table 13: Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to Complete Attack Resolution Within 24 hours

	Sebetralstat 300 mg (n=87 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)
Time to complete attack resolution ^a (hours) n (%)	37 (42.5)	46 (49.5)	23 (27.4)
Q1 (95% CI)	8.58 (4.08, 13.13)	7.54 (3.78, 9.55)	22.78 (9.79, NE)
Median (95% CI)	NE (16.60, NE)	24.00 (10.60, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Nominal <i>P</i> -value (active vs. placebo)	0.0011	<0.0001	
Adjusted <i>P</i> -value (active vs. placebo)	0.0022	<0.0001	

^aDefined as a PGI-S rating of "None" ≥2 time points in a row

Table 14: Subgroups by Population Characteristics (time to first incidence of decrease in severity)

Time to first incidence of decrease in severity ^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	n	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)
Current HAE treatment						
On-demand with LTP	19	9.27 (1.79, NE)	21	5.53 (2.27, NE)	18	NE (5.57, NE)
On-demand	68	8.45 (3.40, NE)	72	8.15 (2.79, NE)	66	NE (NE, NE)
Age						
Adolescent	10	NE (0.28, NE)	11	NE (0.33, NE)	9	NE (0.56, NE)
Adult	77	8.04 (3.30, NE)	82	7.75 (3.27, NE)	75	NE (NE, NE)
Geography						
US	27	NE (1.33, NE)	28	NE (2.52, NE)	23	NE (7.46, NE)
Europe	44	8.45 (2.76, NE)	49	3.59 (2.27, 9.62)	48	NE (NE, NE)
Asia/Pacific	16	8.54 (1.27, NE)	16	NE (5.53, NE)	13	NE (0.78, NE)
Category	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Diagnosis						
HAE Type 1	79	9.32 (1.53-NE)	87	6.53 (2.19-NE)	79	NE (5.57-NE)
HAE Type 2	8	4.76 (1.33-NE)	6	NE (2.23-NE)	5	NE (NE-NE)
Sex						
Female	54	10.42 (1.81-NE)	56	8.15 (2.31-NE)	55	NE (7.13-NE)
Male	33	5.21 (1.27-NE)	37	6.53 (1.83-NE)	29	NE (1.76-NE)

^aDefined as ≥1 level decrease on PGI-S ≥2 time points in a row within 12 hours of first study drug administration

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Table 15: Subgroups by Attack Characteristics (time to first incidence of decrease in severity)

Time to first incidence of decrease in severity ^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)

Attack Location						
Laryngeal	2	NE (NE, NE)	2	NE (NE, NE)	4	5.57 (1.76, NE)
Neck and Above	11	NE (0.77, NE)	12	2.90 (0.28, NE)	13	NE (1.27, NE)
Abdominal only	24	4.08 (0.81, NE)	32	5.53 (2.27, 9.62)	29	NE (5.53, NE)
Subcutaneous only	49	9.27 (2.76, NE)	49	NE (3.41, NE)	44	NE (NE, NE)
Abdominal and subcutaneous	10	NE (0.27, NE)	10	1.64 (0.62, NE)	7	6.52 (0.56, NE)
Mucosal (abdomen or larynx/throat)	36	5.53	44	5.21	40	NE
Severity (controlled for baseline)						
Mild	36	NE (NE, NE)	41	NE (NE, NE)	36	NE (NE, NE)
Moderate	35	4.98 (1.33, 10.12)	34	3.27 (2.23, 8.54)	33	NE (4.57, NE)
Severe	12	1.31 (0.28, NE)	16	1.53 (0.79, 2.94)	10	6.81 (0.30, NE)
Time to treatment						
<Median (41 min)	46	8.54 (3.28, NE)	47	9.54 (3.77, NE)	39	NE (9.79, NE)
>Median	40	9.27 (1.81, NE)	46	4.19 (2.27, NE)	45	NE (8.37, NE)
Number of administrations						
1 administration	53	4.42 (1.81, 10.12)	56	5.53 (2.35, 9.62)	37	NE (5.57, NE)
2 administrations	34	NE (8.54, NE)	37	NE (3.77, NE)	47	NE (NE, NE)

^aDefined as ≥ 1 level decrease on PGI-S ≥ 2 time points in a row within 12 hours of first study drug administration

Table 15 shows that, among severe attacks, the median time to a reduction in severity was 1.31 hours for 300mg sebetralstat, 1.53 hours for 600mg sebetralstat and 6.81 hours for placebo.

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Figure 17 is a graph showing proportion of attacks reaching reduction in attack severity (PGI-S) with 1 or 2 administrations of sebetralstat.

Table 15A: Proportion of Attacks Reaching Reduction in Attack Severity (PGI-S) With 1 vs 2 Doses

Number of attacks reaching reduction in attack severity within 12 hours, n (%)	Sebetralstat 300 mg (n = 44, 50.6%)*	Sebetralstat 600 mg (n = 49, 52.7%)*
Reached without second dose	40 (90.9)	47 (95.9)
Reached after second dose	4 (9.1)	2 (4.1)

*Proportion of attacks reaching end point within 12 hours

- 5 The proportions of attacks reaching a reduction in severity without a second dose were 90.9% and 95.9% with sebetralstat 300mg and 600mg, respectively.

Table 16: Subgroups by Population Characteristics (time to complete attack resolution)

Time to complete attack resolution ^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	n	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)
Current HAE treatment						
On-demand with LTP	19	17.05 (10.55, NE)	21	19.24 (5.03, NE)	18	16.49 (7.46, NE)
On-demand	68	NE (22.9, NE)	72	NE (10.52, NE)	66	NE (NE, NE)
Age						
Adolescent	10	NE (3.28, NE)	11	NE (0.33, NE)	9	NE (1.55, NE)
Adult	77	NE (16.60, NE)	82	21.02 (10.59, NE)	75	NE (NE, NE)
Geography						
US	27	NE (10.55, NE)	28	21.46 (13.02, NE)	23	NE (14.38, NE)
Europe	44	NE (22.90, NE)	49	NE (9.62, NE)	48	NE (NE, NE)
Asia/Pacific	16	18.94 (4.08, NE)	16	9.11 (3.30, NE)	13	NE (15.10, NE)
Category	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Diagnosis						
HAE Type 1	79	NE (7.52-NE)	87	21.46 (7.29-NE)	79	NE (22.78-NE)
HAE Type 2	8	24.00 (13.33-NE)	6	NE (7.69-NE)	5	NE (NE-NE)
Sex						
Female	54	NE (7.07-NE)	56	22.51 (7.54->24)	55	NE (15.10-NE)

Male	33	NE (9.57-NE)	37	24.00 (6.11-NE)	29	NE (NE-NE)
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^aDefined as a PGI-S of "None" within 24 hours of first study drug administration

Table 17: Subgroups by Attack Characteristics (time to complete attack resolution)

Time to complete attack resolution ^a	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
Category	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)
Attack Location						
Laryngeal	2	NE (NE, NE)	2	NE (NE, NE)	4	8.28 (1.76, NE)
Neck and Above	11	23.49 (1.20, NE)	12	7.29 (2.52, NE)	13	NE (1.27, NE)
Abdominal only	24	NE (4.08, NE)	32	17.45 (6.53, NE)	29	NE (NE, NE)
Subcutaneous only	49	NE (10.58, NE)	49	NE (15.17, NE)	44	NE (NE, NE)
Abdominal and subcutaneous	10	NE (13.13, NE)	10	9.42 (1.32, NE)	7	NE (6.23, NE)
Mucosal (abdomen or larynx/throat)	36	NE	44	15.58	40	NE
Severity (controlled for baseline)						
Mild	36	NE (8.62, NE)	41	18.78 (8.29, NE)	36	NE (NE, NE)
Moderate	35	NE (13.67, NE)	34	16.80 (7.75, NE)	33	NE (NE, NE)
Severe	12	NE (2.46, NE)	16	NE (NE, NE)	10	NE (3.78, NE)
Time to treatment						
<Median (41 min)	46	NE (10.58, NE)	47	15.17 (7.76, NE)	39	NE (NE, NE)
>Median	40	NE (13.67, NE)	46	NE (10.59, NE)	45	NE (NE, NE)
Number of administrations						
1 administration	53	14.98 (5.67, NE)	56	12.83 (7.76, 21.46)	37	NE (7.46, NE)

2 administrations	34	NE (NE, NE)	37	NE (24.00, NE)	47	NE (NE, NE)
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^aDefined as a PGI-S of "None" within 24 hours of first study drug administration

Figure 17 is a graph showing proportion of attacks reaching complete attack resolution (PGI-S) with 1 or 2 administrations of sebetralstat.

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Table 17A: Proportion of Attacks Reaching Complete Attack Resolution (PGI-S) With 1 vs 2 Doses

Number of attacks reaching complete attack resolution within 24 hours, n (%)	Sebetralstat 300 mg (n = 37, 42.5%)*	Sebetralstat 600 mg (n = 46, 49.5%)*
Reached without second dose	34 (91.9)	39 (84.8)
Reached after second dose	3 (8.1)	7 (15.2)

*Proportion of attacks reaching end point within 24 hours

The proportions of attacks that reached complete attack resolution without a second dose were 91.9% and 84.8% with sebetralstat 300mg and 600mg, respectively.

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Correlation of time to treatment with attack duration sub-analysis

The relationship between time from attack onset to treatment and time from treatment to complete attack resolution ("None" on Patient Global Impression of Severity scale within 24 hours) was evaluated in sebetralstat-treated attacks using Cox proportional hazards models adjusted for sequence, period, and baseline attack severity.

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For this analysis, attacks treated with sebetralstat 300 mg or 600 mg were grouped into those that received treatment "earlier" versus "later":

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- "Earlier" treatment was defined as treatment in the first quartile of time to treatment, i.e., those attacks in which sebetralstat was administered on or before 6 minutes from onset of attack.
- "Later" treatment was defined as treatment in the fourth quartile of time to treatment, i.e., those attacks in which sebetralstat was administered on or after 140 minutes from onset of attack.

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The median time from attack onset to treatment administration was 41 minutes (IQR, 6-140).

Figure 22 shows that 79 attacks were treated within 6 minutes.

Table 17B: Demographics and Disease Characteristics of Participants Treating Attacks with Sebetralstat Earlier and Later

	Participants treating “earlier” ^a (n=39)	Participants treating “later” ^a (n=29)
Age, median, years (IQR)	35 (23-48)	35 (21-49)
Sex, female, n (%)	26 (66.7)	16 (55.2)
BMI, median, kg/m ² (IQR)	27.7 (23.68-34.58)	26.8 (23.05-31.65)
Race, n (%)		
White	32 (82.1)	23 (79.3)
Asian	5 (12.8)	3 (10.3)
Black or African American	0	1 (3.4)
Other or not reported	2 (5.1)	2 (6.9)
HAE-C1INH type, n (%)		
Type 1	36 (92.3)	27 (93.1)
Type 2	3 (7.7)	2 (6.9)
Time since HAE-C1INH diagnosis, median, years (IQR)	12.0 (7.0-24.0)	12.1 (6.2-18.0)
Current treatment regimen, n (%)		
On-demand only	30 (76.9)	25 (86.2)
On-demand + LTP	9 (23.1)	4 (13.8)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

5 ^a Due to the crossover design of the study, participants may be represented in both categories for different attacks.

These data show that sebetralstat enabled patients to treat attacks early.

Table 17C: Characteristics of Sebetralstat-treated Attacks

	Attacks treated “earlier” (n=55)	Attacks treated “later” (n=44)
Baseline PGI-S category, n (%) ^{a,b}		
Mild	28 (50.9)	11 (25.0)
Moderate	15 (27.3)	25 (56.8)
Severe/very severe	11 (20.0) ^c	8 (18.2)
Baseline pooled attack location, n (%) ^{a,c,d}		
Mucosal	23 (41.8)	17 (38.6)
Larynx/throat	2 (3.6)	2 (4.5)

Subcutaneous	43 (78.2)	35 (79.5)
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PGL-S, Patient Global Impression of Severity.

^a Participants who had multiple attack locations were counted once in each reported location.

^b None, n (%) = 0 earlier, 1 (1.3) later; Missing, n (%) = 1 (1.8) earlier, 0 later.

^c All attack locations and severities were included except for laryngeal attacks that were considered severe at baseline.

5 ^d Missing, n (%) = 1 (1.8) earlier, 0 later.

The largest proportion of sebetralstat-treated attacks treated “earlier” were mild at baseline, whereas the largest proportion of attacks treated “later” were moderate at baseline (Table 17C).

10 Among 179 attacks treated with sebetralstat (300 or 600 mg), complete attack resolution was achieved faster and more often for attacks treated earlier ($\leq Q1$, median: 17.1 hours; event rate: 50.9%) than for attacks treated later ($\geq Q3$, median: >24 hours; event rate: 29.5%). These data demonstrate that earlier administration of sebetralstat is correlated with a faster time to complete attack resolution.

15 The hazard ratio (95% CI) for $\leq Q1$ vs. $\geq Q3$ was 2.72 (1.33–5.59), indicating a higher probability for faster complete attack resolution for attacks treated earlier. Figure 23 shows that the probability for shorter attack duration was higher when attacks were treated earlier versus later.

Figure 24 shows that a greater proportion of attacks reached complete attack resolution within 24 hours
20 when sebetralstat was administered “earlier” compared to “later”.

When modelled as a continuous variable, the relationship between time to treatment and time to complete attack resolution was 0.88 (95% CI, 0.79-0.97), indicating earlier treatment was correlated with earlier attack resolution.

25

Figure 25 shows that complete attack resolution was reached faster in attacks that were treated earlier.

These data show that complete attack resolution was reached faster and in a greater proportion in attacks that were treated with sebetralstat “earlier” (≤ 6 minutes) compared with those that were treated “later”
30 (≥ 140 minutes). Further, these data show that attacks that were treated earlier were more likely to be mild than attacks treated later.

Secondary Endpoints

35 HAE attacks treated with both 300mg and 600mg of sebetralstat achieved a significantly faster time to a $\geq 50\%$ reduction in composite VAS score within 12 hours ($p=0.0002$ for 300mg sebetralstat and $p=0.0006$

for 600mg sebetralstat) and within 24 hours ($p=0.0001$ for 300mg sebetralstat and $p<0.0001$ for 600mg sebetralstat)

The median time to a $\geq 50\%$ decrease from baseline in the composite VAS score within 12 hours was 6.81 hours with sebetralstat 300 mg, 7.49 hours with sebetralstat 600 mg, and >12 hours with placebo.

The median time to a $\geq 50\%$ decrease from baseline in the composite VAS score within 24 hours was 7.28 hours with sebetralstat 300 mg, 7.55 hours with sebetralstat 600 mg, and >24 hours with placebo.

Figure 8 is a graph showing the cumulative % of patients with a 50% reduction in composite VAS score within 24 hours of IMP administration. Figure 8 shows that the time to 50% reduction in composite VAS score was faster for both 300mg and 600mg sebetralstat compared to placebo.

Table 18: Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to at Least 50% Decrease on Composite VAS from Baseline Within 12 hours

Within 12 Hours of First Study Drug Administration	Sebetralstat 300 mg (n=87 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)
Time to at least 50% decrease on composite VAS from baseline			
Q1 (95% CI)	2.37 (1.87, 3.77)	2.78 (1.79, 3.79)	6.23 (2.95, NE)
Median (95% CI)	6.81 (3.84, NE)	7.49 (5.28, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Nominal <i>P</i> -value (active vs. placebo)	0.0002	0.0006	

Table 19: Linear Mixed Model of Gehan Score and Kaplan-Meier of Time to at Least 50% Decrease on Composite VAS from Baseline Within 24 hours

Within 24 Hours of First Study Drug Administration	Sebetralstat 300 mg (n=87 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=84 attacks)
Time to at least 50% decrease on composite VAS from baseline			
Q1 (95% CI)	2.40 (1.87, 3.80)	2.79 (1.79, 3.88)	6.35 (2.95, 13.12)

Median (95% CI)	7.28 (3.95, 17.24)	7.55 (5.36, 13.37)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Nominal <i>P</i> -value (active vs. placebo)	0.0001	<0.0001	

VAS, Visual Analog Scale

Extent of Drug Exposure

5 Table 20: Extent of Drug Exposure

	Sebetralstat 300 mg (n=86 attacks)	Sebetralstat 600 mg (n=93 attacks)	Placebo (n=83 attacks)
Number of administrations received			
n	86	95	83
Mean (SD)	1.4 (0.49)	1.4 (0.49)	1.6 (0.50)
Median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Number of attacks treated with, n (%)			
1 administration	53 (61.6)	56 (58.9)	37 (44.6)
2 administrations	33 (38.4)	39 (41.1)	46 (55.4)
Time between first and second dose (hours)			
n	28	35	39
Mean (SD)	8.6 (10.1)	7.7 (10.5)	5.1 (4.9)
Median (Q1, Q3)	3.9 (3.3, 8.3)	3.8 (3.3, 6.1)	3.5 (3.2, 4.7)
Minimum, maximum	2.8, 42.1	3.00, 45.3	2.4, 28.3

Use of Conventional Treatment

Table 21: Conventional Treatment Use

	Sebetralstat 300 mg (N=87 Attacks)	Sebetralstat 600 mg (N=93 Attacks)	Placebo (N=84 Attacks)
Conventional treatment use, n (%)			
Within 12 hours	12 (13.8)	8 (8.6)	21 (25.0)

Within 24 hours	18 (20.7)	9 (9.7)	27 (32.1)
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Severity sub-group analysis

Severe and very severe

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Table 22: Time to Beginning of Symptom Relief within 12 Hours of First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Severe and very severe			
Number of IMP-treated HAE attacks	14	18	13
Event	11 (78.6)	15 (83.3)	4 (30.8)
Censored	3 (21.4)	3 (16.7)	9 (69.2)
Censored - Conventional Treatment used	2 (66.7)	1 (33.3)	5 (55.6)
Censored - Lack of post-baseline assessment			1 (11.1)
Censored - No event before 12 hours	1 (33.3)	2 (66.7)	3 (33.3)
Time (hour) to beginning of symptom relief			
25th Percentile (95% CI)	0.8 (0.28, 1.30)	0.8 (0.28, 1.31)	2.7 (0.28, -)
Median (95% CI)	1.4 (0.78, 2.78)	1.5 (0.79, 2.27)	- (0.77, -)
75th Percentile (95% CI)	2.8 (1.30, -)	3.0 (1.68, -)	- (- , -)

Table 23: Time to First Incidence of Decrease from Baseline within 12 Hours of the First IMP

10 Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Severe and very severe			
Number of IMP-treated HAE attacks	14	18	13
Event	11 (78.6)	16 (88.9)	7 (53.8)
Censored	3 (21.4)	2 (11.1)	6 (46.2)

Censored - Conventional Treatment used	2 (66.7)	1 (50.0)	4 (66.7)
Censored - Lack of post-baseline assessment			1 (16.7)
Censored - No event before 12 hours	1 (33.3)	1 (50.0)	1 (16.7)
Time (hour) to first incidence of decrease from baseline			
25th Percentile (95% CI)	0.8 (0.27, 1.28)	0.8 (0.28, 1.31)	1.2 (0.30, 5.53)
Median (95% CI)	1.3 (0.31, 2.78)	1.3 (0.78, 2.27)	6.2 (0.36, -)
75th Percentile (95% CI)	2.8 (1.28, -)	3.0 (1.38, -)	- (5.53, -)

Table 24: Time to HAE Attack Resolution within 24 Hours of the First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Severe and very severe			
Number of IMP-treated HAE attacks	14	18	13
Event	5 (35.7)	4 (22.2)	4 (30.8)
Censored	9 (64.3)	14 (77.8)	9 (69.2)
Censored - Conventional Treatment used	3 (33.3)	3 (21.4)	6 (66.7)
Censored - No event before 24 hours	6 (66.7)	11 (78.6)	3 (33.3)
Time (hour) to HAE attack resolution			
25th Percentile (95% CI)	17.1 (2.27, -)	-(1.32, -)	14.4 (3.78, -)
Median (95% CI)	-(4.69, -)	-(- , -)	-(13.02, -)
75th Percentile (95% CI)	-(- , -)	-(- , -)	-(- , -)

5 Moderate

Table 25: Time to Beginning of Symptom Relief within 12 Hours of First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
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Baseline PGI-S = Moderate			
Number of IMP-treated HAE attacks	35	34	33
Event	26 (74.3)	22 (64.7)	17 (51.5)
Censored	9 (25.7)	12 (35.3)	16 (48.5)
Censored - Conventional Treatment used	4 (44.4)	2 (16.7)	5 (31.3)
Censored - Lack of post-baseline assessment	3 (33.3)	6 (50.0)	4 (25.0)
Censored - No event before 12 hours	2 (22.2)	4 (33.3)	7 (43.8)
Time (hour) to beginning of symptom relief			
25th Percentile (95% CI)	0.8 (0.34, 1.28)	1.3 (0.31, 1.77)	1.3 (0.78, 1.78)
Median (95% CI)	1.6 (0.85, 3.60)	2.1 (1.31, 2.79)	2.1 (1.32, -)
75th Percentile (95% CI)	8.0 (1.79, -)	5.9 (2.21, -)	- (5.57, -)

Table 26: Time to First Incidence of Decrease from Baseline within 12 Hours of the First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Moderate			
Number of IMP-treated HAE attacks	35	34	33
Event	23 (65.7)	20 (58.8)	13 (39.4)
Censored	12 (34.3)	14 (41.2)	20 (60.6)
Censored - Conventional Treatment used	5 (41.7)	3 (21.4)	5 (25.0)
Censored - Lack of post-baseline assessment	3 (25.0)	5 (35.7)	4 (20.0)
Censored - No event before 12 hours	4 (33.3)	6 (42.9)	11 (55.0)
Time (hour) to first incidence of decrease from baseline			
25th Percentile (95% CI)	1.1 (0.77, 2.27)	2.2 (0.79, 2.35)	2.8 (0.78, 7.58)
Median (95% CI)	5.0 (1.33, 10.12)	3.3 (2.23, 8.54)	- (4.57, -)
75th Percentile (95% CI)	- (6.09, -)	- (4.61, -)	- (- , -)

Table 27: Time to HAE Attack Resolution within 24 Hours of the First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Moderate			
Number of IMP-treated HAE attacks	35	34	33
Event	14 (40.0)	19 (55.9)	8 (24.2)
Censored	21 (60.0)	15 (44.1)	25 (75.8)
Censored - Conventional Treatment used	8 (38.1)	4 (26.7)	8 (32.0)
Censored - Lack of post-baseline assessment	2 (9.5)	3 (20.0)	2 (8.0)
Censored - No event before 24 hours	11 (52.4)	8 (53.3)	15 (60.0)
Time (hour) to HAE attack resolution			
25th Percentile (95% CI)	13.1 (2.74, 16.60)	7.5 (3.27, 10.52)	23.1 (8.28, -)
Median (95% CI)	- (13.67, -)	16.8 (7.75, -)	- (- , -)
75th Percentile (95% CI)	- (- , -)	- (19.02, -)	- (- , -)

5 Mild

Table 28: Time to Beginning of Symptom Relief within 12 Hours of First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Mild			
Number of IMP-treated HAE attacks	36	41	36
Event	29 (80.6)	34 (82.9)	19 (52.8)
Censored	7 (19.4)	7 (17.1)	17 (47.2)
Censored - Conventional Treatment used	2 (28.6)	2 (28.6)	5 (29.4)
Censored - Lack of post-baseline assessment	3 (42.9)	1 (14.3)	3 (17.6)

Censored - No event before 12 hours	2 (28.6)	4 (57.1)	9 (52.9)
Time (hour) to beginning of symptom relief			
25th Percentile (95% CI)	0.8 (0.28, 1.28)	1.1 (0.78, 1.31)	2.3 (0.78, 3.28)
Median (95% CI)	1.7 (0.84, 2.28)	1.8 (1.30, 2.78)	7.2 (2.59, -)
75th Percentile (95% CI)	3.5 (2.27, -)	4.0 (2.27, -)	- (- , -)

Table 29: Time to First Incidence of Decrease from Baseline within 12 Hours of the First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Mild			
Number of IMP-treated HAE attacks	36	41	36
Event	10 (27.8)	13 (31.7)	6 (16.7)
Censored	26 (72.2)	28 (68.3)	30 (83.3)
Censored - Conventional Treatment used	5 (19.2)	3 (10.7)	8 (26.7)
Censored - Lack of post-baseline assessment	2 (7.7)	1 (3.6)	2 (6.7)
Censored - No event before 12 hours	19 (73.1)	24 (85.7)	20 (66.7)
Time (hour) to first incidence of decrease from baseline			
25th Percentile (95% CI)	8.5 (3.28, -)	9.1 (2.79, -)	- (6.23, -)
Median (95% CI)	- (- , -)	- (- , -)	- (- , -)
75th Percentile (95% CI)	- (- , -)	- (- , -)	- (- , -)

5 Table 30: Time to HAE Attack Resolution within 24 Hours of the First IMP Administration by Baseline PGI-S and Treatment. Full Analysis Set (N=110)

Parameters	Sebetralstat 300 mg (N=87)	Sebetralstat 600 mg (N=93)	placebo (N=84)
Baseline PGI-S = Mild			
Number of IMP-treated HAE attacks	36	41	36
Event	18 (50.0)	23 (56.1)	10 (27.8)

Censored	18 (50.0)	18 (43.9)	26 (72.2)
Censored - Conventional Treatment used	8 (44.4)	2 (11.1)	12 (46.2)
Censored - Lack of post-baseline assessment		1 (5.6)	1 (3.8)
Censored - No event before 24 hours	10 (55.6)	15 (83.3)	13 (50.0)
Time (hour) to HAE attack resolution			
25th Percentile (95% CI)	5.2 (1.81, 9.54)	5.5 (2.79, 9.14)	17.9 (6.23, -)
Median (95% CI)	- (8.62, -)	18.8 (8.29, -)	- (- , -)
75th Percentile (95% CI)	- (- , -)	- (- , -)	- (- , -)

These data confirm that sebetralstat is effective at treating a wide range of attack severities, including severe and very severe attacks.

5 Hazard Ratios

Figure 18 is a graph showing hazard ratios of sebetralstat 600 mg compared with 300 mg for primary or key secondary endpoints by baseline attack severity. Figure 19 is a graph showing hazard ratios of sebetralstat 600 mg compared with 300 mg for primary or key secondary endpoints by treatment paradigm.

Table 30A: Hazard Ratios of Sebetralstat 600 mg Compared with 300 mg for Primary or Key Secondary Endpoints

	Endpoint		
Hazard Ratio (95% CI)	Time to beginning of symptom relief within 12 hours	Time to reduction in severity within 12 hours	Time to complete attack resolution within 24 hours
All attacks	1.09 (0.77, 1.53)	0.94 (0.62, 1.43)	0.80 (0.52, 1.25)
Attacks by baseline severity (PGI-S)			
None ^a /mild	1.16 (0.69, 1.95)	0.97 (0.39, 2.42)	0.83 (0.43, 1.58)
Moderate	1.27 (0.70, 2.32)	1.17 (0.63, 2.17)	0.62 (0.29, 1.32)
Severe/very severe	1.64 (0.53, 5.12)	1.28 (0.48, 3.41)	2.45 (0.48, 12.57)

Attacks by treatment paradigm			
On-demand only	1.15 (0.78, 1.70)	0.97 (0.60, 1.55)	0.70 (0.41, 1.19)
On-demand with LTP ^b	1.13 (0.55, 2.32)	0.88 (0.35, 2.24)	1.08 (0.45, 2.61)

^aFor 2 attacks in the placebo group, participants rated the baseline attack severity as “None” on the PGI-S rating scale. These attacks were censored at zero for both key secondary endpoints.

^bOf the 24 participants taking LTP, 11 (46%) received berotralstat, 8 (33%) received lanadelumab, and 5 (21%) received C1INH.

5 Safety

Sebetralstat was safe and well-tolerated with a safety profile comparable with placebo. There were no serious adverse events reported in the trial and no patients withdrew due to adverse events.

10

Table 31: Reason for Discontinuation

Reasons for Discontinuation	Total (N=110)
Total Discontinuations	10
Adverse event	0
Death	0
Protocol violation	1
Lost to follow-up	2
Physician decision	1
Withdrawal by patient	3
Other	3

Table 32: On-Treatment Treatment-Emergent Adverse Events

Number of patients, n (%) E	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=93)	Placebo (n=83)
Any TEAE	5 (5.8) 5	6 (6.5) 6	10 (12.0) 13
Any treatment-related TEAE	2 (2.3) 2	2 (2.2) 2	4 (4.8) 5
Any Grade 3 or higher TEAE	0	0	0
Any treatment-related Grade 3 or higher TEAE	0	0	0
Any serious TEAE	0	0	0
Any treatment-related serious TEAE	0	0	0
Any TEAE leading to hospitalization	0	0	0

Any TEAE leading to study discontinuation	0	0	0
Any TEAE leading to death	0	0	0

Table 32A: Safety Summary by Number of Doses Administered

Variable – no. (%)	Sebetralstat				Placebo	
	300 mg (n = 58)	300 mg + 300 mg (n = 28)	600 mg (n = 60)	600 mg + 600 mg (n = 34)	1 administration (n = 44)	2 administrations (n = 39)
Any TEAE	10 (17.2)	7 (25.0)	7 (11.7)	7 (20.6)	5 (11.4)	12 (30.8)
Treatment-related	2 (3.4)*	0	1 (1.7)*	2 (5.9)*	3 (6.8)*	1 (2.6)*
Serious TEAE [†]	1 (1.7) [‡]	0	2 (3.3)	0	0	0
Treatment-related	0	0	0	0	0	0
Severe TEAE [§]	1 (1.7) [‡]	0	0	0	0	0
Treatment-related	0	0	0	0	0	0
Any TEAE leading to study discontinuation	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0

*Treatment-related TEAEs were fatigue and indigestion with sebetralstat 300 mg, nausea with sebetralstat 600 mg, dyspepsia and hot flash with sebetralstat 600 mg + 600 mg, headache and nausea (same patient), rash, and dysgeusia with 1 administration of placebo, and irregular menstruation with 2 administrations of placebo.

[†]Serious TEAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event by medical and scientific judgement.

[‡]The severe TEAE and serious TEAE listed are the same event; lumbar disc herniation that required hospitalization and was deemed severe by the investigator.

[§]Severe TEAE was defined as a qualitative assessment of an AE of grade 3 severity by the investigator or as reported by the patient.

Table 33: On-Treatment Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

System organ class preferred term, n (%) E	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=93)	Placebo (n=83)
Eye disorders	0	0	1 (1.2) 1
Eye hemorrhage	0	0	1 (1.2) 1
Gastrointestinal disorders	3 (3.5) 3	2 (2.2) 2	3 (3.6) 3
Vomiting	1 (1.2) 1	1 (1.1) 1	1 (1.2) 1
Nausea	0	1 (1.1) 1	1 (1.2) 1
Abdominal pain	0	0	1 (1.2) 1
Dyspepsia	1 (1.2) 1	0	0
Gingival bleeding	1 (1.2) 1	0	0

General disorders and administration site conditions	1 (1.2) 1	0	1 (1.2) 1
Fatigue	1 (1.2) 1	0	1 (1.2) 1
Infections and infestations	1 (1.2) 1	0	2 (2.4) 2
Influenza	0	0	1 (1.2) 1
Pharyngitis bacterial	0	0	1 (1.2) 1
Pharyngitis streptococcal	1 (1.2) 1	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (1.2) 1
Neck pain	0	0	1 (1.2) 1
Nervous system disorders	0	4 (4.3) 4	2 (2.4) 2
Headache	0	3 (3.2) 3	1 (1.2) 1
Dizziness	0	1 (1.1) 1	0
Dysgeusia	0	0	1 (1.2) 1
Reproductive system and breast disorders	0	0	1 (1.2) 1
Menstruation irregular	0	0	1 (1.2) 1
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.2) 1
Epistaxis	0	0	1 (1.2) 1
Skin and subcutaneous tissue disorders	0	0	1 (1.2) 1
Rash	0	0	1 (1.2) 1

Second Dose Endpoint Medians

Table 34: Second Dose Endpoint Medians

Category	Sebetralstat 300 mg		Sebetralstat 600 mg		Placebo	
	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)	# Attacks	Median (95% CI)
Time to beginning of symptom relief						
1 administration	53	1.30 (0.81, 1.77)	56	1.38 (1.02, 1.81)	37	2.30 (1.30, 6.23)
2 administrations	34	2.36 (1.29, 7.55)	37	2.97 (1.83, 9.53)	47	NE (3.60, NE)
Time to first incidence of decrease in severity						

1 administration	53	4.42 (1.81, 10.12)	56	5.53 (2.35, 9.62)	37	NE (5.57, NE)
2 administrations	34	NE (8.54, NE)	37	NE (3.77, NE)	47	NE (NE, NE)
Time to complete attack resolution						
1 administration	53	14.98 (5.67, NE)	56	12.83 (7.76, 21.46)	37	NE (7.46, NE)
2 administrations	34	NE (NE, NE)	37	NE (24.00, NE)	47	NE (NE, NE)

Analysis Sets

Table 35: Analysis sets

Patients, n (%)	Sequence A (N=23)	Sequence B (N=21)	Sequence C (N=23)	Sequence D (N=23)	Sequence E (N=23)	Sequence F (N=23)	Total (N=136)
Safety set	18 (78.3)	18 (85.7)	15 (65.2)	17 (73.9)	20 (87.0)	22 (95.7)	110 (80.9)
Full analysis set (FAS)	18 (78.3)	18 (85.7)	15 (65.2)	17 (73.9)	20 (87.0)	22 (95.7)	110 (80.9)
Per-protocol set	14 (60.9)	16 (76.2)	11 (47.8)	12 (52.2)	15 (65.2)	18 (78.3)	86 (63.2)
On-demand FAS	15 (65.2)	13 (61.9)	12 (52.2)	14 (60.9)	17 (73.9)	15 (65.2)	86 (63.2)
Prophylaxis FAS	3 (13.0)	5 (23.8)	3 (13.0)	3 (13.0)	3 (13.0)	7 (30.4)	24 (17.6)

5 Sequence A: Placebo/Sebetralstat 600 mg/Sebetralstat 300 mg; Sequence B: Placebo/Sebetralstat 300 mg/Sebetralstat 600 mg; Sequence C: Sebetralstat 600 mg/Sebetralstat 300 mg/Placebo; Sequence D: Sebetralstat 300 mg/Placebo/Sebetralstat 600 mg; Sequence E: Sebetralstat 600 mg/Sebetralstat 300 mg/Placebo; Sequence F: Sebetralstat 600 mg/Placebo/Sebetralstat 300 mg.

These results demonstrate that sebetralstat is safe and effective at treating HAE attacks.

10

Example 5 – Open-label extension Phase 3 study

An Open-label Extension Trial to Evaluate the Long-term Safety of 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.

15

Clinicaltrials.gov identifier: NCT05505916.

Objectives:

5 *Primary Objective:*

- To assess the safety of long-term administration of sebetralstat in adolescent and adult patients with hereditary angioedema (HAE) type I or II.

Secondary Objectives:

- 10
- To assess the long-term efficacy of sebetralstat in the treatment of 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.

15 Overall Design

This is an open-label, multicenter extension trial to evaluate the long-term safety of sebetralstat in patients who are 12 years of age or older with HAE type I or II. This trial is being 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 2 years.

20

On-Demand Treatment of HAE Attacks

Patients take a single dose of 600 mg sebetralstat (i.e. 2 x 300 mg tablets) to treat each HAE attack.

25

Patients are permitted to take a second dose of 600 mg sebetralstat separated by at least 3 hours following the first dose if attack symptoms persist without improvement. Conventional on-demand treatment may be used upon patients' discretion and in consultation with their physician.

Laryngeal attacks may be treated with the IMP in this trial; all patients are instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsen after initial treatment with IMP.

30

Short-term Prophylactic Therapy

Patients can use sebetralstat as short-term prophylactic therapy prior to undergoing surgical, dental, or medical procedures. The decision to use sebetralstat for short-term prophylactic therapy is made on a case-by-case basis, after consultation with the Investigator and the patient, and based on whether treatment with sebetralstat for short-term prophylactic therapy is medically appropriate for the patient.

Patients are permitted to take up to a maximum of 3 doses of sebetralstat in a 24-hour period as short-term prophylaxis, with each dose approximately 6 hours apart, starting approximately 1 hour prior to the start of the procedure. sebetralstat cannot be used for short-term prophylaxis if the patient had an attack within the last 48 hours or has not completed their last eDiary assessment for that attack.

Short-term prophylactic therapy must stop if an HAE attack occurs that is treated with IMP or conventional on-demand treatment. If the attack starts within 24 hours of the start of the procedure, the patient should treat the attack with conventional on-demand treatment. If the attack starts >24 hours after the start of the procedure, sebetralstat may be used.

Efficacy analyses

Efficacy endpoints are as follows:

1. PGI-C: HAE attacks with symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of initial dose of IMP administration.
2. PGI-S: HAE attacks with any decrease from baseline within 12 hours of initial dose of IMP administration.
3. PGI-S: HAE attacks that resolved, defined as “none” within 24 hours of initial dose of IMP administration.
4. AE-QoL (exploratory): AE-QoL change over time.

Efficacy endpoints related to HAE attacks (endpoints 1 through 3) are summarized by proportions (number of HAE attacks that meet the endpoint [endpoints 1 through 3] that occur in patients from the FAS divided by the total number of HAE attacks across all patients in the FAS).

Endpoint AE-QoL (4) are summarized as a continuous variable over time.

For each patient, the time observed in the trial, the number of HAE attacks experienced, the number of IMP-treated attacks (single-dose and two doses) and the number of attacks treated with conventional on-demand treatment are described, alongside the characteristics of the attacks (location, severity). This is summarized for all patients in the FAS.

5

For all procedures where sebetralstat was used as short-term prophylaxis, the proportion that did not result in an HAE attack within 24 hours after the start of the procedure is summarized.

Primary Outcome Measures:

10

1. Frequencies and percentages of patients with AEs, AEs within 2 days of IMP administration, serious AE's and AEs causing premature discontinuation.

[Time Frame: AEs will be recorded from the first dose of IMP in the trial up to and including the end of study (EOS) visit, a maximum of 2 years for each patient.]

15

2. Number and percentage of patients with normal or abnormal laboratory results at each scheduled visit.

[Time Frame: Throughout the duration of the trial.]

20

3. Number and percentage of patients with normal or abnormal vital sign results at each scheduled visit

[Time Frame: Throughout the duration of the trial.]

Secondary Outcome Measures:

25

1. Patient Global Impression of Change (PGI-C).

[Time Frame: within 12 hours of initial dose of IMP administration.]

time to beginning of symptom relief defined as at least "a little better" (2 time points in a row)

30

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

[Time Frame: within 12 hours of initial dose of IMP administration.]

3. PGI-S: time to HAE attack resolution

35

[Time Frame: within 24 hours of initial dose of IMP administration.]

PGI-S: time to HAE attack resolution, defines as "none".

For more information, see clinical trial NCT05505916.

5

Interim results from the open-label extension

Table 5.1: Patient Demographics and Disease-specific History

	All participants (N=84)
Age, median, years (IQR)	35.0 (22.0, 47.0)
Age group, n (%)	
<18 years	12 (14.3)
≥18 years	72 (85.7)
Sex, female, n (%)	54 (64.3)
Race, n (%)	
White	63 (75.0)
Asian	12 (14.3)
Other	2 (2.4)
Not reported	7 (8.3)
BMI, median, kg/m ² (IQR)	25.6 (22.3, 31.1)
HAE-C1INH type, n (%)	
Type 1	77 (91.7)
Type 2	7 (8.3)
Current treatment regimen, n (%)	
On-demand only	59 (70.2)
On-demand with LTP ^a	25 (29.8)

BMI, body mass index; HAE-C1INH; hereditary angioedema with C1-inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
^aOf the 25 participants using LTP, 13 (52%) used berotralstat, 5 (20%) used lanadelumab, and 7 (28%) used C1-inhibitor agents.

10

15

640 of attacks were treated with sebetralstat (Table 5.2).

Table 5.2: Baseline Attack Characteristics

	Sebetralstat-treated attacks (N=640)
Primary attack locations, ^{a,b} n (%)	
Abdomen	244 (38.1)
Arms/hands	190 (29.7)
Legs/feet	154 (24.1)
Head/face/neck	56 (8.8)
Torso	43 (6.7)
Genitals	37 (5.8)
Larynx/throat	14 (2.2)
Primary pooled attack locations, n (%)	
Mucosal	257 (40.2)
Laryngeal	14 (2.2)
Subcutaneous	376 (58.8)
Baseline PGI-S category, ^c n (%)	
Mild	192 (30.0)
Moderate	277 (43.3)
Severe/Very severe	160 (25.0)

^aPatients with multiple attack locations were counted once in each reported location.

^bMissing, n (%) = 7 (1.1).

^cNone, n (%) = 4 (0.6); Missing, n (%) = 7 (1.1).

5

Sebetralstat exposure

Participants treated a median of five attacks with sebetralstat (IQR, 2 to 8; range, 1 to 37; Figure 20).

Twenty participants treated at least nine attacks.

10

Figure 20 is a graph showing the number of sebetralstat-treated attacks in the open-label extension Phase 3 study of sebetralstat.

The median time from attack recognition to treatment was 9 minutes (IQR, 1 to 69; Figure 21).

Fourteen laryngeal attacks (2.2%) were treated with sebetralstat, with a median time from onset of attack to first administration of 8.0 minutes (IQR, 1.0 to 27.0).

Figure 21 is a graph showing the time from attack recognition to sebetralstat administration in the open-label extension Phase 3 study of sebetralstat.

Table 5.3: Safety

Number of participants, n (%)	All participants (N=84)
Any TEAE	47 (56.0)
Treatment-related	8 (9.5)
Serious TEAE ^a	3 (3.6)
Treatment-related	0
Severe TEAE ^b	5 (6.0)
Treatment-related	1 (1.2)
Any TEAE leading to permanent discontinuation	4 (4.8)
Treatment-related	2 (2.4)
Any TEAE leading to death	0

TEAE, treatment-emergent adverse event.

^aSerious TEAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event by medical and scientific judgment.

^bSevere (grade 3 or 4) TEAEs were evaluated by investigators according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (US Department of Health and Human Services. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007. Accessed April 30, 2024. <https://www.fda.gov/media/73679/download>).

Table 5.4: Treatment-related TEAEs

Number of participants, n (%)	All participants (N=84)
Treatment-related TEAE	8 (9.5)
Gastrointestinal disorders	

Number of participants, n (%)	All participants (N=84)
Diarrhea	1 (1.2)
Nausea	1 (1.2)
Vomiting	1 (1.2)
General disorders	
Influenza like illness	1 (1.2)
Muskuloskeletal and connective tissue disorders	
Arthralgia	1 (1.2)
Nervous system disorders	
Headache	3 (3.6)
Tremor	1 (1.2)
Skin and subcutaneous tissue disorders	
Skin burning sensation	1 (1.2)
Urticaria	1 (1.2)

Efficacy

486 attacks (75.9%) were treated with one dose of sebetralstat. Conventional on-demand treatments were utilized for 36 attacks (5.6%) within 12 hours of the first dose of sebetralstat.

- Regardless of the number of attacks treated using sebetralstat, efficacy was maintained. Median time to beginning of symptom relief for the first nine sebetralstat-treated attacks were 1.66, 1.77, 1.79, 2.79, 1.86, 1.93, 1.77, 2.35, and 1.77 hours.

Efficacy in the subset of laryngeal attacks (n=14) is presented in Table 36.

Table 5.5: Efficacy Results

	Sebetralstat-treated attacks (N=640)
Time to beginning of symptom relief within 12 hours, h	
Median	1.80
IQR	0.95 to 5.45

	Sebetralstat-treated attacks (N=640)
Time to reduction in attack severity within 12 hours, h	
Median	6.57
IQR	1.61 to >12
Time to complete resolution within 24 hours, h	
Median	21.02
IQR	7.22 to >24

IQR, interquartile range.

449 attacks (94.3%) reached beginning of symptom relief without a second dose or before a second dose was administered. The proportions of attacks that reached reduction in severity and complete resolution without a second dose or before a second dose was administered were 95.5% and 85.7%,
5 respectively.

Table 36: Time to Beginning of Symptom Relief within 12 Hours of First IMP Administration, Time to Reduction in Attack Severity within 12 hours of First IMP Administration, and Time to Complete Resolution within 24 hours of First IMP Administration Full Analysis Set - Subject with Laryngeal Attacks only (N=14)

Parameters	Statistics
Number of Laryngeal Attacks	14
Events	10 (71.4)
Censored	4 (28.6)
Conventional medication taken on or before 12 hours post IMP admin	1 (25.0)
No symptom relief on or before 12 hours post IMP administration	3 (75.0)
Time (hour) to Beginning of Symptom Relief	
25th Percentile (95% CI)	0.5
Median (95% CI)	1.3
75th Percentile (95% CI)	5.3
Time (hour) to reduction in attack severity within 12 hours	
25th Percentile	0.8
Median	1.5

75th Percentile	6.1
Time (hour) to complete resolution within 24 hours	
25th Percentile	1.8
Median	6.8
75th Percentile	24

Among laryngeal attacks, the median time to symptom relief was 1.3 hours.

In sebetralstat-treated laryngeal attacks, time to beginning of symptom relief was consistent with that
5 observed across all attacks; reduction in attack severity and complete resolution were reached faster in
laryngeal attacks than in other attack locations.

These results further confirm that sebetralstat is effective in treating laryngeal attacks.

10 Additional, updated data for sebetralstat-treated laryngeal attacks is provided in Tables 5.16-5.18.

Pooled data for attacks involving the larynx from Example 4 and Example 5

This analysis evaluated the effectiveness of sebetralstat as an on-demand treatment for attacks involving
15 the larynx using pooled data from the phase 3 trial described in Example 4 (NCT05259917) and the open-
label extension phase 3 study described in Example 5 (NCT05505916).

16 attacks involving the larynx in 8 participants were treated with sebetralstat 600 mg in the trials in
Examples 4 and 5 (Table 5.6).

20

Table 5.6: Participant Demographics and Disease Characteristics

	Participants with ≥1 attacks involving the larynx ^a (n=8)
Age, median (IQR), years	35.5 (26.5-57.0)
Sex, female, n (%)	6 (75.0)
BMI, median (IQR), kg/m ²	29.7 (23.6-31.1)
Race, n (%)	
White	8 (100)
HAE-C1INH type, n (%)	

Type 1	8 (100)
Time since HAE-C1INH diagnosis, median (IQR), years	18.1 (6.0-26.0)
Current treatment regimen, n (%)	
On-demand only	4 (50.0)
On-demand + LTP ^b	4 (50.0)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

^a Includes participants who experienced an attack involving the larynx treated with sebetralstat 600 mg in Example 4 or Example 5.

^b The LTP agents were lanadelumab (n=2) and berotralstat (n=2).

5

At baseline, 12 (75%) attacks were affecting the larynx only and 4 (25%) attacks were affecting the larynx and other locations.

Figure 26 shows that most (68.9%) attacks involving the larynx had a PGI-S rating of moderate (43.8%), severe (18.8%), or very severe (6.3%) at baseline.

10

Figure 27 shows that the median time to oral sebetralstat administration to treat an attack involving the larynx was 8 minutes (IQR: 1-30).

15 Table 5.7: Primary and Secondary Endpoints

	All attacks treated with 600mg sebetralstat in Example 4 (n=93)	All attacks treated with 600mg sebetralstat in Example 5 (n=640)	Attacks involving the larynx treated with 600mg sebetralstat in Example 4 and Example 5 (n=16)
Time to beginning of symptom relief, ^a median (IQR), hours	1.79 (1.02-3.79)	1.80 (0.95-5.45)	1.52 (0.69-6.07)
Time to reduction in severity, ^b median (IQR), hours	7.75 (2.19->12)	6.57 (1.61->12)	1.69 (0.81-6.82)
Time to complete attack resolution, ^c median (IQR), hours	24.00 (7.54->24)	21.02 (7.22->24)	9.74 (1.78->24)

IQR, interquartile range; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

^a Defined as a PGI-C of at least "A Little Better" for 2 consecutive time points within 12 hours.

^b Defined as a decrease in the PGI-S rating for 2 consecutive time points within 12 hours.

^c Defined as a PGI-S of "None" within 24 hours.

20

The efficacy of sebetralstat in treating attacks involving the larynx was consistent with that observed for all attacks in both Example 4 and Example 5 (Table 5.7).

In attacks involving the larynx, the median time to beginning of symptom relief was 1.52 hours (IQR: 0.69-6.07), the median time to reduction in severity was 1.69 hours (IQR: 0.81-6.82), and median time to complete attack resolution was 9.74 hours (IQR: 1.78->24).

Table 5.8: Administration of Conventional On-demand Treatment or an Additional Dose of Sebetralstat

	All attacks treated with 600mg sebetralstat in Example 4 (n=93)	All attacks treated with 600mg sebetralstat in Example 5 (n=640)	Attacks involving the larynx treated with 600mg sebetralstat in Example 4 and Example 5 (n=16)
Additional administration of sebetralstat through 24 hours ^a	37 (39.8)	154 (24.1)	7 (43.8)
Conventional on-demand treatment ^{b,c}	8 (8.6)	36 (5.6)	2 (12.5) ^d

Values are in n (%).

^a Participants were instructed to administer the optional additional dose of sebetralstat 600 mg ≥3 hours after the first dose. In Example 4, a second administration of study treatment was not permitted for attacks involving the larynx. However, a second administration of sebetralstat 600 mg was permitted for attacks involving the larynx in Example 5.

^b Attacks involving the larynx could be treated with conventional on-demand treatment at any time and all participants were instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsened following initial study treatment.

^c Includes conventional on-demand treatment administered within 12 hours of first administration sebetralstat 600 mg in Example 4 or Example 5.

^d One participant reported administering conventional on-demand treatment one minute after sebetralstat administration (the endpoint was censored at 12 hours). One participant met the primary endpoint 1.26 hours after administering sebetralstat but reported administering conventional on-demand treatment 11.7 hours after administering sebetralstat.

Figure 28 shows that over 81.8% of attacks involving the larynx that reached the primary and key secondary endpoints did so without administration of an additional dose of sebetralstat. Specifically, the proportion of attacks that reached the beginning of symptom relief without a second dose was 81.8%, the proportion of attacks that reached a reduction in severity without a second dose was 90.0% and the proportion of attacks that reached complete attack resolution without a second dose was 88.9%.

Table 5.9: Safety

	Participants with ≥1 attacks involving the larynx ^a (n=8)
Any TEAE	2 (25.0)
Treatment-related	0
Serious TEAE	1 (12.5)
Treatment-related	0
Severe TEAE	2 (25.0)
Treatment-related	0
Adverse event during treatment that led to study discontinuation	0
Adverse event during treatment that led to death	0

TEAE, treatment-emergent adverse event. Values are in n (%).

^a Includes participants who experienced an attack involving the larynx treated with sebetralstat 600 mg in Example 4 or Example 5.

5 There were no serious or severe treatment-related adverse events in participants who experienced an attack involving the larynx. There were no reports of dysphagia associated with administration of study drug for any attacks involving the larynx.

10 These pooled data show that sebetralstat enabled rapid treatment of attacks involving the larynx in patients with HAE.

15 Further, this pooled analysis shows that the efficacy of sebetralstat in attacks involving the larynx was comparable with that observed in all sebetralstat-treated attacks and that most attacks involving the larynx treated with sebetralstat 600 mg did not require the use of a second dose to achieve efficacy endpoints.

Subgroup analyses of treatment of HAE attacks in patients receiving long-term prophylaxis (LTP), in particular berotralstat

20 Updated data gathered from the open-label extension phase 3 study (NCT05505916) are described below.

Subgroup analysis of treatment of HAE attacks in patients receiving LTP

35 participants receiving LTP experienced 504 attacks of which 382 (76%) were treated with sebetrastat. Of these, 16 participants receiving berotralstat treated 178 attacks, 13 participants receiving lanadelumab treated 80 attacks, and 6 participants receiving C1INH replacement treated 124 attacks. Participants receiving LTP experienced a mean (SD) of 1.71 (1.48) attacks per month (berotralstat: 1.8 (1.2); lanadelumab: 1.2 (0.8); C1-INH: 2.5 (2.1)).

The median time to treatment was 6 minutes (IQR, 1-40) (berotralstat: 20.0 minutes (1.0-67.0); lanadelumab: 11.0 minutes (1.0-50.0); C1-INH: 1.0 minutes (0.0-7.0)).

At the time of treatment, the mean (SD) Patient Global Impression of Severity (PGI-S) score was 2.0 (1.0) (berotralstat: 2.1 (1.0); lanadelumab: 1.8 (0.7); C1-INH: 2.1 (1.0)).

The median (IQR) attack frequency was 1.0 (0.6 to 2.7) attacks per month in participants receiving LTP, 1.2 (0.6 to 3.4) attacks per month in participants receiving berotralstat, 0.8 (0.7 to 1.0) attacks per month in participants receiving lanadelumab, and 2.1 (1.2 to 2.7) attacks per month in participants receiving C1INH replacement.

Table 5.10: Patient Demographics

	Participants receiving LTP (N = 35)
Age, median (IQR), years	44.0 (28.0 to 56.0)
Age group, n (%)	
≥12 to <18 years	5 (14.3)
≥18 years	30 (85.7)
Sex, female, n (%)	27 (77.1)
Race, n (%)	
White	25 (71.4)
Asian	8 (22.9)
Other or multiple	1 (2.9)
Not reported	1 (2.9)
BMI, median (IQR), kg/m ²	26.6 (22.1 to 33.1)
LTP treatment regimen	

Plasma kallikrein inhibitors	83%
C1-INH	17%
HAE-C1INH type, n (%)	
Type 1	31 (88.6)
Type 2	4 (11.4)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

Table 5.11: Baseline Attack Characteristics

	Sebetralstat-treated attacks (N=382)
Baseline PGI-S category	
Mild	32%
Moderate	41%
Severe/very severe	27%
Baseline pooled attack location	
Subcutaneous	46%
Mucosal (Larynx)	54% (4.9%)

5

Table 5.12: Efficacy Results

	Sebetralstat-treated attacks (N=382)
Time to beginning of symptom relief within 12 hours, h	
Median	1.3
IQR	0.8 to 3.8
Time to reduction in attack severity within 12 hours, h	
Median	4.2
IQR	1.3 to >12
Time to complete resolution within 24 hours, h	
Median	14.8
IQR	4.6 to >24

No evidence of a diminished response over successive treatments of attacks was observed.

Figure 29 shows that sebetralstat was effective in treating HAE attacks and provided fast symptom relief in participants having attacks whilst on LTP.

The median time to beginning of symptom relief was 1.3 hours (0.8-3.8) for participants receiving LTP, 1.3 hours (0.4-2.5) for participants receiving berotralstat, 1.3 hours (1.2-1.6) for participants receiving lanadelumab, and 1.8 hours (1.3->12) for participants receiving C1-INH. These data show that sebetralstat enabled rapid treatment of HAE attacks and effective as an oral, on-demand treatment among patients receiving berotralstat, lanadelumab or C1-INH for LTP.

In 85 of 382 attacks (22.3%) a second dose of sebetralstat was administered within 12 hours. 264 attacks (69.1%) reached beginning of symptom relief within 12 hours. Of these, 90.5% achieved this endpoint before or without a second dose of sebetralstat. These data show that most attacks treated with sebetralstat in participants who were receiving LTP did not require the use of a second dose of sebetralstat to achieve efficacy endpoints.

Conventional on-demand treatment was administered within 12 hours in 20 of 382 attacks (5.2%) treated with sebetralstat in participants who were receiving LTP. In 16 of these 20 attacks, conventional on-demand treatment was administered after 1 dose of sebetralstat. These data show that most attacks treated with sebetralstat in participants who were receiving LTP did not require conventional on-demand treatment.

Among those receiving LTP, 5 participants (14%) experienced 8 treatment-emergent adverse events (TEAEs) that were considered treatment related. No serious treatment-related TEAEs occurred.

These data further confirm that sebetralstat is effective as an oral on-demand treatment for HAE attacks occurring among patients receiving LTP. In addition, sebetralstat was generally well tolerated and no new safety signals were observed in participants who were receiving LTP with berotralstat, lanadelumab, or C1INH replacement.

Subgroup analysis of treatment of HAE attacks in patients receiving berotralstat

16 participants receiving berotralstat for LTP experienced 239 attacks of which 178 (75%) were treated with sebetralstat. Participants experienced a mean (SD) of 1.79 (1.41) attacks per month.

The median (IQR) attack frequency was 1.2 (0.6 to 3.4) attacks per month in participants who were receiving berotralstat.

The median time to treatment was 20 minutes (IQR, 1-67).

5

Table 5.13: Patient Demographics

	Patients receiving berotralstat (N = 16)
Age, median (IQR), years	38.5 years (21.0 to 48.0)
Age group, n (%)	
≥12 to <18 years	4 (25.0)
≥18 years	12 (75.0)
Sex, female, n (%)	13 (81.3)
Race, n (%)	
White	10 (62.5)
Asian	4 (25.0)
Other or multiple	1 (6.3)
Not reported	1 (6.3)
BMI, median (IQR), kg/m ²	27.1 (21.6 to 33.8)
HAE-C1INH type, n (%)	
Type 1	15 (93.8)
Type 2	1 (6.3)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

10 Table 5.14: Baseline Attack Characteristics

	Sebetralstat-treated attacks (N=178)
Baseline PGI-S category	
Mild	33%
Moderate	36%
Severe/very severe	30%
Baseline pooled attack location	
Subcutaneous	39%
Mucosal (Larynx)	61% (4.5%)

Table 5.15: Efficacy Results

	Sebetralstat-treated attacks (N=178)
Time to beginning of symptom relief within 12 hours, h	
Median	1.3
IQR	0.4 to 2.5
Time to reduction in attack severity within 12 hours, h	
Median	2.7
IQR	0.9 to >12
Time to complete resolution within 24 hours, h	
Median	10.9
IQR	3.0 to >24

No evidence of a diminished response over successive treatments of attacks was observed.

- 5 These data show that sebetralstat enabled rapid on-demand treatment of attacks and provided fast symptom relief in participants having attacks whilst on berotralstat.

Figure 30 shows that sebetralstat was effective in treating HAE attacks and provided fast symptom relief in participants who were receiving berotralstat as LTP.

10

In 38 of 178 attacks (21.3%) a second dose of sebetralstat was administered within 12 hours. 139 attacks (78.1%) reached beginning of symptom relief within 12 hours. Of these, 92.1% achieved this endpoint before or without a second dose of sebetralstat. These data show that most attacks treated with sebetralstat in participants who were receiving berotralstat as LTP did not require the use of a second

15

Conventional on-demand treatment was administered within 12 hours in 8 of 178 attacks (4.5%). In 5 of these 8 attacks, conventional on-demand treatment was administered after 1 dose of sebetralstat.

These data show that most attacks treated with sebetralstat in patients who were receiving berotralstat as LTP did not require conventional on-demand treatment.

20

Among those receiving berotralstat, 12 participants experienced 63 treatment-emergent adverse events (TEAEs), with 6 (10%) considered treatment related. No serious treatment-related TEAEs occurred. These data confirm that sebetralstat was well-tolerated, and no new safety signals were observed in patients receiving berotralstat.

5

These data further confirm that sebetralstat is well-tolerated and effective as an oral on-demand treatment of HAE attacks occurring among patients receiving oral berotralstat for LTP.

Further updated data gathered from the open-label extension phase 3 study (NCT05505916) are described below.

10 Subgroup analysis of treatment of HAE attacks involving the larynx

137 participants treated 1706 attacks with sebetralstat. 32 (1.9%) of these 1706 attacks involved the larynx. The median time from attack onset to treatment was 11.5 minutes (IQR, 1.0 to 34.0) for attacks involving the larynx.

15

Table 5.16: Participant Demographics and Disease-specific History

	All participants (N = 134)	Participants experiencing attacks involving the larynx (n = 16)
Age, median (IQR), years	35.0 (21.0 to 49.0)	44.5 (29.5 to 59.5)
Age group, n (%)		
≥12 to <18 years	23 (17.2)	2 (12.5)
≥18 to <65 years	107 (79.9)	13 (81.3)
≥65 years	4 (3.0)	1 (6.3)
Sex, female, n (%)	87 (64.9)	10 (62.5)
Race, n (%)		
White	99 (73.9)	13 (81.3)
Asian	17 (12.7)	2 (12.5)
Other or multiple	11 (8.2)	-
Not reported	7 (5.2)	1 (6.3)
BMI, median (IQR), kg/m ²	25.4 (22.3 to 30.6)	29.6 (26.4 to 32.2)
HAE-C1INH type, n (%)		

Type 1	125 (93.3)	16 (100)
Type 2	9 (6.7)	-
Current treatment regimen, n (%)		
On-demand only	99 (73.9)	9 (56.3)
LTP + on-demand	35 (26.1) ^a	7 (43.8)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

^aOf the 35 participants using LTP, 29 (21.6%) used kallikrein inhibitors (berotralstat or lanadelumab) and 6 (4.5%) used C1INH replacement.

5 Table 5.17: Baseline Attack Characteristics

	All attacks treated with sebetralstat (N = 1706)	Attacks involving the larynx treated with sebetralstat (n = 32)
Baseline PGI-S category, ^a n (%)		
Mild	589 (34.5)	7 (21.9)
Moderate	685 (40.2)	15 (46.9)
Severe/very severe	330 (19.3)	9 (28.1)
Time from attack onset to treatment administration, median (IQR), minutes	10.0 (1.0 to 68.5)	11.5 (1.0 to 34.0)

IQR, interquartile range; PGI-S, Patient Global Impression of Severity.

^aMissing: n (%) = 73 (4.3) for all attacks; None: n (%) = 29 (1.7) for all attacks, 1 (3.1) for attacks involving the larynx treated with sebetralstat.

These data show that sebetralstat enabled early treatment of attacks involving the larynx (median 11.5 minutes).

10

Table 5.18: Efficacy Results for Attacks Involving the Larynx

	Attacks involving the larynx treated with sebetralstat (n = 32)
Time to beginning of symptom relief within 12 hours, h	
Median	1.27
IQR	0.76 to 2.87
Time to reduction in attack severity within 12 hours, h	
Median	4.25

	Attacks involving the larynx treated with sebetralstat (n = 32)
IQR	1.22 to >12
Time to complete resolution within 24 hours, h	
Median	12.69
IQR	5.11 to >24

These data show that sebetralstat enabled rapid treatment of mild to very severe attacks involving the larynx and provided rapid symptom relief.

- 5 Figure 31 shows that sebetralstat was effective in treating HAE attacks involving the larynx.

4 of the 32 attacks involving the larynx (12.5%) were treated with a second administration of sebetralstat within 12 hours and 3 (9.4%) were treated with conventional treatment within 12 hours. Conventional treatment was administered after a single administration of sebetralstat in 2 attacks.

- 10 Conventional treatment was administered in 1 attack after 2 administrations of sebetralstat.

- 15 Of attacks reaching beginning of symptom relief within 12 hours (89.3%), 96.0% did so before or without an additional sebetralstat administration. These data show that most attacks involving the larynx treated with sebetralstat did not require the use of a second dose of sebetralstat to achieve efficacy endpoints.

These data further confirm that sebetralstat is effective and well-tolerated as an oral on-demand treatment for HAE attacks involving the larynx.

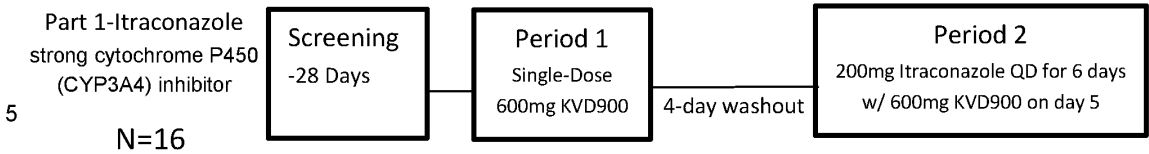
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Example 6 – Drug-Drug interaction studies

Study 1 (strong CYP3A4 inhibitors and inducers)

- 25 This was an open-label, multiple-part, two-period clinical trial. Screening of participants occurred within 28 days prior to the first dosing.

Strong CYP3A4 inhibitor (itraconazole)



10 Subjects received a single dose of 600mg sebetralstat alone and in combination with 200mg itraconazole to investigate the effect of strong CYP3A4 inhibition on the single-dose pharmacokinetics (PK) of sebetralstat.

15 On Day 1 of Period 1, subjects were administered a single dose of 600mg sebetralstat. In Period 2, subjects were administered 200mg itraconazole once daily (QD) for 6 consecutive days, with a single dose of 600mg Sebetralstat co-administered on Day 5. There was a washout of at least 4 days between the dose in Period 1 and the first dose of itraconazole in Period 2.

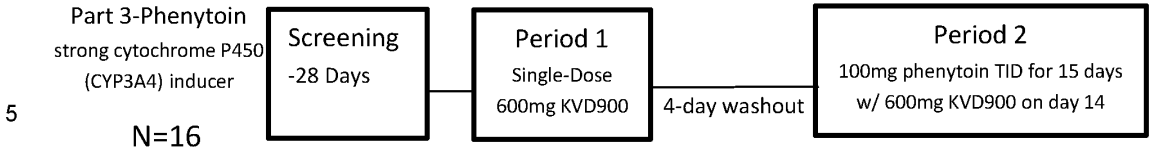
20 Figures 9 and 10 are graphs showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inhibitor itraconazole. Figures 9 and 10 illustrate that administration of itraconazole with sebetralstat resulted in a greater than two-fold increase in C_{max} compared to administration of sebetralstat alone.

Table 37: PK data

	Sebetralstat Alone	Sebetralstat + Itraconazole
C_{max} ng/mL [95% CI]	5593 [4102-7084]	11799 [10851-12748]
T_{max}	0.75	1.5
AUC_{inf} ng*h/mL [95% CI]	18039 [12732-23347]	85904 [74671-97138]
AUC_{0-12} ng*h/mL	15721	64217

25 Administration of itraconazole with sebetralstat resulted in a greater than two-fold increase in C_{max} and an approximately five-fold increase in AUC_{inf} .

Strong CYP3A4 inducer (3-phenytoin)



Subjects received a single dose of 600mg sebetralstat alone and in combination with 100mg phenytoin to investigate the effect of strong CYP3A4 induction on the single-dose PK of sebetralstat.

10

On Day 1 of Period 1, subjects were administered a single dose of 600mg sebetralstat. In Period 2, subjects were administered an oral dose of 100mg phenytoin three times daily (TID) for 15 consecutive days, with a single oral dose of 600mg Sebetralstat co-administered with the first phenytoin dose on Day 14. There was a washout of at least 4 days between the dose in Period 1 and the first dose of phenytoin in Period 2.

15

Figures 11 and 12 are graphs showing the plasma concentration of sebetralstat when administered alone and with the strong CYP3A4 inducer phenytoin. Figures 11 and 12 show that administration of phenytoin with sebetralstat resulted in a significant reduction in C_{max} compared to administration of sebetralstat alone.

20

Table 38: PK data

	Sebetralstat Alone	Sebetralstat + Phenytoin
C_{max} ng/mL [95% CI]	5623 [3929-7316]	1904 [1341-2468]
T_{max}	0.75	0.63
AUC_{inf} ng*h/mL [95% CI]	19104 [15340-22869]	3272 [2530-4013]
AUC_{0-12} ng*h/mL	16542	3123

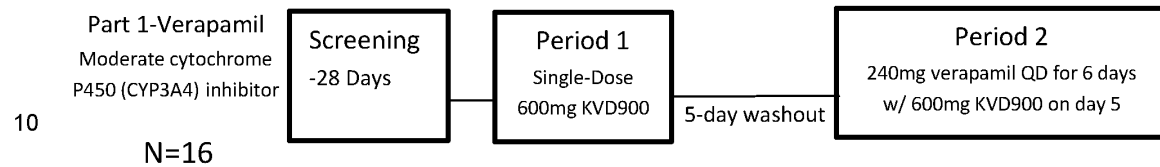
Administration of phenytoin with sebetralstat resulted in large reductions to both C_{max} (approximately three-fold) and AUC_{inf} (approximately six-fold).

25

Study 2 (moderate CYP3A4 inhibitors and inducers)

This was an open-label, multiple-part, two-period clinical trial. Screening of participants occurred within 28 days prior to the first dosing.

5

Part 1: Moderate CYP3A4 inhibitor (verapamil)

Subjects received a single dose of 600mg sebetralstat alone and in combination with 240mg verapamil to investigate the effect of moderate CYP3A4 inhibition on the single-dose PK of sebetralstat.

15

On Day 1 of Period 1, subjects were administered a single dose of 600mg sebetralstat. In Period 2, subjects were administered 240mg verapamil QD for 6 days, with a single dose of 600mg sebetralstat co-administered on day 5. There was a washout of at least 5 days between the sebetralstat dose in Period 1 and the first dose of verapamil in Period 2.

20

Figures 13 and 14 are graphs showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inhibitor verapamil. Figures 13 and 14 illustrate that administration of verapamil with sebetralstat resulted in a significant increase in C_{max} compared to administration of sebetralstat alone.

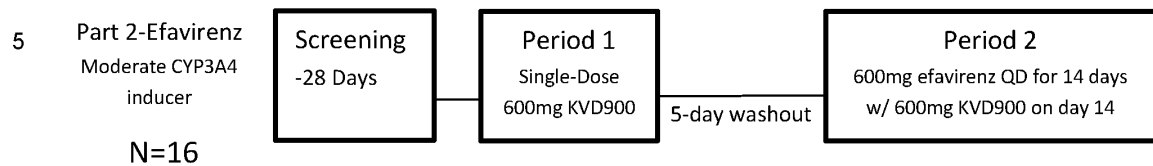
25

Table 39: PK Summary-Moderate Inhibition

Period	Avg C_{max}	C_{max} CV%	C_{max} 95% CI	Geomean C_{max}	Avg AUC_{last}	AUC 95% CI	Geomean AUC_{last}	Median T_{max}
Sebetralstat	5787	54.5	[4106-7467]	5047	20924	[16359-25489]	19436	1.125
Sebetralstat + verapamil	9558	40.73	[7484-11633]	8901	41187	[34466-47907]	39555	1.25

Table 40: PK comparison between sebetralstat + verapamil and sebetralstat alone

C_{max} GMR	Estimate	90% CI
Sebetralstat + verapamil vs. sebetralstat	1.764	[1.47, 2.116]
AUC_{last} GMR	Estimate	90% CI
Sebetralstat + verapamil vs. sebetralstat	2.035	[1.830, 2.263]

Part 2: Moderate CYP3A4 inducer (efavirenz)

- 10 Subjects received a single dose of 600mg sebetralstat alone and in combination with 600mg efavirenz to investigate the effect of moderate CYP3A4 induction on the PK of sebetralstat.

On Day 1 of Period 1, subjects were administered a single dose of 600mg sebetralstat. In Period 2, subjects were administered 600mg efavirenz QD for 14 days, with a single dose of 600mg sebetralstat co-

15 administered on day 14. There was a washout of at least 5 days between the sebetralstat dose in Period 1 and the first dose of efavirenz in Period 2.

Figures 15 and 16 are graphs showing the plasma concentration of sebetralstat when administered alone and with the moderate CYP3A4 inducer efavirenz. Figures 15 and 16 illustrate that administration of

20 efavirenz with sebetralstat resulted in a significant reduction in C_{max} compared to administration of sebetralstat alone.

Table 41: PK Summary-Moderate Induction

Period	Avg C_{max}	C_{max} CV%	C_{max} 95% CI	Geomean C_{max}	Avg AUC_{last}	AUC 95% CI	Geomean AUC_{last}	Median T_{max}
Sebetralstat	5398	45.31	[4094-6701]	4758	19639	[15861-23418]	18423	1.125
Sebetralstat + efavirenz	2193	58.67	[1480-2905]	1743	4393	[3101-5684]	3828	1

Table 42: PK comparison between sebetralstat + efavirenz and sebetralstat alone

C_{max} GMR	Estimate	90% CI
Sebetralstat + efavirenz vs. sebetralstat	0.367	[0.281, 0.479]
AUC_{last} GMR	Estimate	90% CI
Sebetralstat + efavirenz vs. sebetralstat	0.212	[0.170, 0.263]

Sebetralstat CYP3A4 Victim DDI Summary

5 Table 43: Sebetralstat CYP3A4 Victim DDI Summary

CYP3A4 interaction	C_{max} GMR	C_{max} 90% CI	AUC GMR^b	AUC 90%CI
Strong Inhibition	2.354	[1.932, 2.868]	5.211	[4.553, 5.964]
Moderate Inhibition ^a	1.764	[1.470, 2.116]	2.035	[1.830, 2.263]
Strong Induction	0.336	[0.245, 0.462]	0.164	[0.136, 0.198]
Moderate Induction ^a	0.367	[0.281, 0.479]	0.212	[0.170, 0.263]

^a Preliminary

^b Derived from AUC_{last}

These data demonstrate that a drug-drug interaction occurs when sebetralstat is administered with a strong or moderate CYP3A4 inhibitor or a CYP3A4 inducer.

10

EMBODIMENTS

Treatment of severe or worse HAE attacks

- 5 1. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.
- 10 2. The method according to embodiment 1, wherein sebetralstat is in free base form.
- 10 3. The method according to embodiment 1 or 2, wherein the HAE attack is characterised as “severe” according to the PGI-S scale.
- 15 4. The method according to embodiment 1 or 2, wherein the HAE attack is characterised as “very severe” according to the PGI-S scale.
- 15 5. The method according to any of embodiments 1 to 4, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
- 20 6. The method according to embodiment 5, wherein the first dose is administered on-demand upon recognition of a symptom of an HAE attack.
- 20 7. The method according to embodiment 5, wherein the first dose is administered on-demand at the earliest recognition of an HAE attack.
- 25 8. The method of embodiment 5, wherein the first dose is administered on-demand for the treatment of patient-recognized attacks of HAE.
- 25 9. The method according to any of embodiments 5 to 8, wherein the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack.
- 30 10. The method according to embodiment 9, wherein the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.
- 30 11. The method according to any of embodiments 5 to 10, wherein the attack is resolved without administering a second dose to the patient.
- 35 12. The method according to any of embodiments 5 to 10, wherein the patient is administered a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
- 35 13. The method according to embodiment 12, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose.

14. The method according to embodiment 13, wherein the second dose is administered about 3 hours after the first dose.
15. The method according to any of embodiments 12 to 14, wherein the attack is resolved without administering a third dose to the patient.
- 5 16. The method according to any of embodiments 12 to 14, wherein the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
17. The method according to embodiment 16, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose.
- 10 18. The method according to embodiment 17, wherein the third dose is administered about 3 hours after the second dose.
19. The method according to any of embodiments 16 to 18, wherein the attack is resolved without administering a fourth dose to the patient.
20. The method according to any of embodiments 16 to 18, wherein the patient is administered a
15 fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
21. The method according to embodiment 20, wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose.
22. The method according to embodiment 21, wherein the fourth dose is administered about 3
20 hours after the third dose.
23. The method according to any of embodiments 20 to 22, wherein the attack is resolved without administering any further dose to the patient.
24. The method according to any of embodiments 5 to 23, wherein each dose is administered as one tablet.
- 25 25. The method according to any of embodiments 1 to 24, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as part of a pharmaceutical composition.
26. The method according to any of embodiments 1 to 25, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as an oral dosage form
30 comprising: (i) sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and (ii) at least one pharmaceutically acceptable excipient.
27. The method according to embodiment 26, wherein the oral dosage form is a tablet.
28. The method according to embodiment 27, wherein the tablet is a film-coated tablet.
29. The method according to embodiment 27, wherein the tablet is an orodispersible tablet.

30. The method according to any of embodiments 1 to 29, wherein the attack is resolved without administering a second treatment to the patient.
31. The method according to any of embodiments 1 to 30, wherein the patient is aged 12 years and above.
- 5 32. The method according to embodiment 31, wherein the patient is aged between 12 and less than 18.
33. The method according to embodiment 31, wherein the patient is aged 18 years and above.
34. The method according to any of embodiments 1 to 33, wherein the patient is also being treated with a prophylactic treatment of HAE.
- 10 35. The method according to embodiment 34, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.
36. The method according to embodiment 34, wherein the prophylactic treatment is an attenuated androgen.
- 15 37. The method according to embodiment 36, wherein the attenuated androgen is selected from danazol and oxandrolone.
38. The method according to embodiment 34, wherein the prophylactic treatment is tranexamic acid.
39. The method according to embodiment 34, wherein the prophylactic treatment is
20 non-androgen therapy.
40. The method according to embodiment 34, wherein the prophylactic treatment is a C1 inhibitor.
41. The method according to embodiment 34, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.
42. The method according to embodiment 34, wherein the prophylactic treatment is a plasma
25 kallikrein inhibitor.
43. The method according to embodiment 34, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitbant.
44. The method according to embodiment 43, wherein the prophylactic treatment is selected from
30 garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitbant.
45. The method according to embodiment 43, wherein the prophylactic treatment is Cinryze®, Haegarda®, or Berinert®.
46. The method according to embodiment 43, wherein the prophylactic treatment is selected from
35 lanadelumab and berotralstat.

47. The method according to embodiment 46, wherein the prophylactic treatment is lanadelumab.
48. The method according to embodiment 46, wherein the prophylactic treatment is berotralstat.
49. The method according to any one of embodiments 1 to 33, wherein the patient is not also being treated with a prophylactic treatment of HAE.
- 5 50. The method according to any of embodiments 1 to 49, wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an attack of the neck and above that is not a laryngeal attack, an abdominal attack, and a subcutaneous attack.
51. The method according to embodiment 50, wherein the HAE attack is a laryngeal attack.
52. The method according to embodiment 50, wherein the HAE attack is an attack of the neck and
10 above.
53. The method according to embodiment 52, wherein the attack of the neck and above is not a laryngeal attack.
54. The method according to embodiment 50, wherein the HAE attack is an abdominal attack.
55. The method according to embodiment 50, wherein the HAE attack is a subcutaneous attack.
- 15 56. The method according to any of embodiments 1 to 55, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief.
57. The method according to embodiment 56, wherein "symptom relief" means that the attack is rated as "a little better" or higher for two consecutive time points when assessed according to
20 the PGI-C scale.
58. The method according to any of embodiments 1 to 57, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity.
59. The method according to embodiment 58, wherein "reduction in attack severity" means that
25 the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.
60. The method according to any of embodiments 1 to 59, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to achieve complete attack resolution.
- 30 61. The method according to embodiment 60, wherein "complete attack resolution" means the attack severity is rated as "none" on the PGI-S scale.

Treatment of HAE attacks in patients on prophylactic treatment

62. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE.
63. The method according to embodiment 62, wherein sebetralstat is in the free base form.
64. The method according to embodiment 62 or 63, wherein the first dose is administered on-demand upon recognition of a symptom of an HAE attack.
65. The method according to embodiment 62 or 63, wherein the first dose is administered on-demand at the earliest recognition of an HAE attack.
66. The method of embodiment 62 or 63, wherein the first dose is administered on-demand for the treatment of patient-recognized attacks of HAE.
67. The method according to any of embodiments 62 to 66, wherein the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack.
68. The method according to embodiment 67, wherein the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.
69. The method according to any of embodiments 62 to 68, wherein the attack is resolved without administering a second dose to the patient.
70. The method according to any of embodiments 62 to 68, wherein the patient is administered a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
71. The method according to embodiment 70, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose.
72. The method according to embodiment 71, wherein the second dose is administered about 3 hours after the first dose.
73. The method according to any of embodiments 70 to 72, wherein the attack is resolved without administering a third dose to the patient.
74. The method according to any of embodiments 70 to 72, wherein the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
75. The method according to embodiment 74, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose.

76. The method according to embodiment 75, wherein the third dose is administered about 3 hours after the second dose.
77. The method according to any of embodiments 74 to 76, wherein the attack is resolved without administering a fourth dose to the patient.
- 5 78. The method according to any of embodiments 74 to 76, wherein the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
79. The method according to embodiment 78, wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose.
- 10 80. The method according to embodiment 79, wherein the fourth dose is administered about 3 hours after the third dose.
81. The method according to any of embodiments 78 to 80, wherein the attack is resolved without administering any further dose to the patient.
82. The method according to any of embodiments 62 to 81, wherein each dose is administered as
15 one tablet.
83. The method according to any of embodiments 62 to 82, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as part of a pharmaceutical composition.
84. The method according to any of embodiments 62 to 83, wherein sebetralstat (or a
20 pharmaceutically acceptable salt and/or solvate thereof) is administered as an oral dosage form comprising: (i) sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and (ii) at least one pharmaceutically acceptable excipient.
85. The method according to embodiment 84, wherein the oral dosage form is a tablet.
86. The method according to embodiment 85, wherein the tablet is a film-coated tablet.
- 25 87. The method according to embodiment 85, wherein the tablet is an orodispersible tablet.
88. The method according to any of embodiments 62 to 87, wherein the attack is resolved without administering a second treatment to the patient.
89. The method according to any of embodiments 62 to 88, wherein the patient is aged 12 years and above.
- 30 90. The method according to embodiment 89, wherein the patient is aged between 12 and less than 18.
91. The method according to embodiment 89, wherein the patient is aged 18 years and above.
92. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa)
35 binding agent, or a C1INH replacement agent.

93. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is an attenuated androgen.
94. The method according to embodiment 93, wherein the attenuated androgen is selected from danazol, and oxandrolone.
- 5 95. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is tranexamic acid.
96. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is non-androgen therapy.
- 10 97. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is a C1 inhibitor.
98. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.
99. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is a plasma kallikrein inhibitor.
- 15 100. The method according to any of embodiments 62 to 91, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
- 20 101. The method according to embodiment 100, wherein the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
102. The method according to embodiment 100, wherein the prophylactic treatment is Cinryze®, Haegarda®, or Berinert®.
103. The method according to embodiment 100, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.
- 25 104. The method according to embodiment 103, wherein the prophylactic treatment is lanadelumab.
105. The method according to embodiment 103, wherein the prophylactic treatment is berotralstat.
- 30 106. The method according to any of embodiments 62 to 105, wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an attack of the neck and above that is not a laryngeal attack, an abdominal attack, and a subcutaneous attack.
107. The method according to embodiment 106, wherein the HAE attack is a laryngeal attack.
108. The method according to embodiment 106, wherein the HAE attack is an attack of the neck and above.
- 35

109. The method according to embodiment 106, wherein the HAE attack is an abdominal attack.

110. The method according to embodiment 106, wherein the HAE attack is a subcutaneous attack.

111. The method according to any of embodiments 62 to 110, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.

5 112. The method according to embodiment 111, wherein the HAE attack is characterised as “mild” according to the PGI-S scale.

113. The method according to embodiment 111, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.

10 114. The method according to embodiment 113, wherein the HAE attack is characterised as “moderate” according to the PGI-S scale.

115. The method according to embodiment 113, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

116. The method according to embodiment 115, wherein the HAE attack is characterised as “severe” according to the PGI-S scale.

15 117. The method according to embodiment 115, wherein the HAE attack is characterised as “very severe” according to the PGI-S scale.

118. The method according to any of embodiments 62 to 117, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief.

20 119. The method according to embodiment 118, wherein “symptom relief” means that the attack is rated as “a little better” or higher for two consecutive time points when assessed according to the PGI-C scale.

25 120. The method according to any of embodiments 62 to 119, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity.

121. The method according to embodiment 120, wherein “reduction in attack severity” means that the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.

30 122. The method according to any of embodiments 62 to 121, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to achieve complete attack resolution.

123. The method according to embodiment 122, wherein “complete attack resolution” means the attack severity is rated as “none” on the PGI-S scale.

Dosing

124. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
125. The method according to embodiment 124, wherein sebetralstat is in the free base form.
126. The method according to embodiment 124 or 125, wherein the first dose is administered on-demand upon recognition of a symptom of an HAE attack.
127. The method according to embodiment 124 or 125, wherein the first dose is administered on-demand at the earliest recognition of an HAE attack.
128. The method of embodiment 124 or 125, wherein the first dose is administered on-demand for the treatment of patient-recognized attacks of HAE.
129. The method according to any of embodiments 124 to 128, wherein the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack.
130. The method according to embodiment 129, wherein the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.
131. The method according to any of embodiments 124 to 130, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose.
132. The method according to embodiment 131, wherein the second dose is administered about 3 hours after the first dose.
133. The method according to any of embodiments 124 to 132, wherein the attack is resolved without administering a third dose to the patient.
134. The method according to any of embodiments 124 to 132, wherein the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
135. The method according to embodiment 134, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose.

136. The method according to embodiment 135, wherein the third dose is administered about 3 hours after the second dose.
137. The method according to any of embodiments 134 to 136, wherein the attack is resolved without administering a fourth dose to the patient.
- 5 138. The method according to any of embodiments 134 to 136, wherein the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
139. The method according to embodiment 138, wherein the fourth dose is administered between about 2 hours and about 6 hours after the third dose.
- 10 140. The method according to embodiment 139, wherein the fourth dose is administered about 3 hours after the third dose.
141. The method according to any of embodiments 138 to 140, wherein the attack is resolved without administering any further dose to the patient.
142. The method according to any of embodiments 124 to 141, wherein each dose is
15 administered as one tablet.
143. The method according to any of embodiments 124 to 142, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as part of a pharmaceutical composition.
144. The method according to any of embodiments 124 to 143, wherein sebetralstat (or a
20 pharmaceutically acceptable salt and/or solvate thereof) is administered as an oral dosage form comprising: (i) sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and (ii) at least one pharmaceutically acceptable excipient.
145. The method according to embodiment 144, wherein the oral dosage form is a tablet.
146. The method according to embodiment 145, wherein the tablet is a film-coated tablet.
- 25 147. The method according to embodiment 145, wherein the tablet is an orodispersible tablet.
148. The method according to any of embodiments 124 to 147, wherein the attack is resolved without administering a second treatment to the patient.
149. The method according to any of embodiments 124 to 148, wherein the patient is aged
30 12 years and above.
150. The method according to embodiment 149, wherein the patient is aged between 12 and less than 18.
151. The method according to embodiment 149, wherein the patient is aged 18 years and above.

152. The method according to any of embodiments 124 to 151, wherein the patient is also being treated with a prophylactic treatment of HAE.
153. The method according to embodiment 152, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.
154. The method according to embodiment 152, wherein the prophylactic treatment is an attenuated androgen.
155. The method according to embodiment 154, wherein the attenuated androgen is selected from danazol, and oxandrolone.
156. The method according to embodiment 152, wherein the prophylactic treatment is tranexamic acid.
157. The method according to embodiment 152, wherein the prophylactic treatment is non-androgen therapy.
158. The method according to embodiment 152, wherein the prophylactic treatment is a C1 inhibitor.
159. The method according to embodiment 152, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.
160. The method according to embodiment 152, wherein the prophylactic treatment is a plasma kallikrein inhibitor.
161. The method according to embodiment 152, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
162. The method according to embodiment 161, wherein the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
163. The method according to embodiment 161, wherein the prophylactic treatment is Cinryze®, Haegarda®, or Berinert®.
164. The method according to embodiment 161, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.
165. The method according to embodiment 164, wherein the prophylactic treatment is lanadelumab.
166. The method according to embodiment 164, wherein the prophylactic treatment is berotralstat.
167. The method according to any of embodiments 124 to 151, wherein the patient is not already taking a prophylactic treatment of HAE.

168. The method according to any of embodiments 124 to 167, wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an attack of the neck and above that is not a laryngeal attack, an abdominal attack, and a subcutaneous attack.
169. The method according to embodiment 168, wherein the HAE attack is a laryngeal attack.
- 5 170. The method according to embodiment 168, wherein the HAE attack is an attack of the neck and above.
171. The method according to embodiment 168, wherein the HAE attack is an abdominal attack.
172. The method according to embodiment 168, wherein the HAE attack is a subcutaneous
10 attack.
173. The method according to any of embodiments 124 to 172, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.
174. The method according to embodiment 173, wherein the HAE attack is characterised as “mild” according to the PGI-S scale.
- 15 175. The method according to embodiment 173, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.
176. The method according to embodiment 175, wherein the HAE attack is characterised as “moderate” according to the PGI-S scale.
177. The method according to embodiment 175, wherein the HAE attack is characterised as
20 “severe” or above according to the PGI-S scale.
178. The method according to embodiment 177, wherein the HAE attack is characterised as “severe” according to the PGI-S scale.
179. The method according to embodiment 177, wherein the HAE attack is characterised as “very severe” according to the PGI-S scale.
- 25 180. The method according to any of embodiments 124 to 179, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief.
181. The method according to embodiment 180, wherein “symptom relief” means that the attack is rated as “a little better” or higher for two consecutive time points when assessed
30 according to the PGI-C scale.
182. The method according to any of embodiments 124 to 181, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity.

183. The method according to embodiment 182, wherein “reduction in attack severity” means that the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.

5 184. The method according to any of embodiments 124 to 183, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to achieve complete attack resolution.

185. The method according to embodiment 184, wherein “complete attack resolution” means the attack severity is rated as “none” on the PGI-S scale.

10 ***Treatment of HAE attacks of the neck and above***

186. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof
15 on-demand, wherein the HAE attack is an attack of the neck and above.

187. The method according to embodiment 186, wherein sebetralstat is in the free base form.

188. The method according to embodiment 186 or 187, wherein the first dose is administered on-demand upon recognition of a symptom of an HAE attack.

20 189. The method according to embodiment 186 or 187, wherein the first dose is administered on-demand at the earliest recognition of an HAE attack.

190. The method of embodiment 186 or 187, wherein the first dose is administered on-demand for the treatment of patient-recognized attacks of HAE.

25 191. The method according to any of embodiments 186 to 190, wherein the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack.

192. The method according to embodiment 191, wherein the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.
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193. The method according to any of embodiments 186 to 192, wherein the attack is resolved without administering a second dose to the patient.

194. The method according to any of embodiments 186 to 192, wherein the patient is administered a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
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195. The method according to embodiment 194, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose.
196. The method according to embodiment 195, wherein the second dose is administered about 3 hours after the first dose.
- 5 197. The method according to any of embodiments 194 to 196, wherein the attack is resolved without administering a third dose to the patient.
198. The method according to any of embodiments 194 to 196, wherein the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
- 10 199. The method according to embodiment 198, wherein the third dose is administered between about 2 hours and about 6 hours after the second dose.
200. The method according to embodiment 199, wherein the third dose is administered about 3 hours after the second dose.
201. The method according to any of embodiments 198 to 200, wherein the attack is
15 resolved without administering a fourth dose to the patient.
202. The method according to any of embodiments 198 to 200, wherein the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
203. The method according to embodiment 202, wherein the fourth dose is administered
20 between about 2 hours and about 6 hours after the third dose.
204. The method according to embodiment 203, wherein the fourth dose is administered about 3 hours after the third dose.
205. The method according to any of embodiments 202 to 204, wherein the attack is resolved without administering any further dose to the patient.
- 25 206. The method according to any of embodiments 186 to 205, wherein each dose is administered as one tablet.
207. The method according to any of embodiments 186 to 206, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as part of a pharmaceutical composition.
- 30 208. The method according to any of embodiments 186 to 207, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered as an oral dosage form comprising: (i) sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof), and (ii) at least one pharmaceutically acceptable excipient.
209. The method according to embodiment 208, wherein the oral dosage form is a tablet.
- 35 210. The method according to embodiment 209, wherein the tablet is a film-coated tablet.

211. The method according to embodiment 209, wherein the tablet is an orodispersible tablet.
212. The method according to any of embodiments 186 to 211, wherein the attack is resolved without administering a second treatment to the patient.
- 5 213. The method according to any of embodiments 186 to 212, wherein the patient is aged 12 years and above.
214. The method according to embodiment 213, wherein the patient is aged between 12 and less than 18.
- 10 215. The method according to embodiment 213, wherein the patient is aged 18 years and above.
216. The method according to any of embodiments 186 to 215, wherein the patient is also being treated with a prophylactic treatment of HAE.
217. The method according to embodiment 216, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa)
15 binding agent, or a C1INH replacement agent.
218. The method according to embodiment 216, wherein the prophylactic treatment is an attenuated androgen.
219. The method according to embodiment 218, wherein the attenuated androgen is selected from danazol, and oxandrolone.
- 20 220. The method according to embodiment 216, wherein the prophylactic treatment is tranexamic acid.
221. The method according to embodiment 216, wherein the prophylactic treatment is non-androgen therapy.
222. The method according to embodiment 216, wherein the prophylactic treatment is a C1
25 inhibitor.
223. The method according to embodiment 216, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.
224. The method according to embodiment 216, wherein the prophylactic treatment is a plasma kallikrein inhibitor.
- 30 225. The method according to embodiment 216, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
226. The method according to 225, wherein the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®,
35 or Haegarda®), donidalorsen, and deucricitibant.

227. The method according to embodiment 225, wherein the prophylactic treatment is Cinryze®, Haegarda®, or Berinert®.
228. The method according to 225, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.
- 5 229. The method according to embodiment 228, wherein the prophylactic treatment is lanadelumab.
230. The method according to embodiment 228, wherein the prophylactic treatment is berotralstat.
- 10 231. The method according to any of embodiments 186 to 215, wherein the patient is not also being treated with a prophylactic treatment of HAE.
232. The method according to any of embodiments 186 to 231, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.
233. The method according to embodiment 232, wherein the HAE attack is characterised as “mild”, according to the PGI-S scale.
- 15 234. The method according to embodiment 232, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.
235. The method according to embodiment 234, wherein the HAE attack is characterised as “moderate”, according to the PGI-S scale.
- 20 236. The method according to embodiment 234, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.
237. The method according to embodiment 236, wherein the HAE attack is characterised as “severe”, according to the PGI-S scale.
238. The method according to embodiment 236, wherein the HAE attack is characterised as “very severe”, according to the PGI-S scale.
- 25 239. The method according to any of embodiments 186 to 238, wherein the attack of the neck and above is not a laryngeal attack.
240. The method according to embodiment 239, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) slows the progression of the attack into a laryngeal attack.
- 30 241. The method according to embodiment 239, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) reduces the severity of any resulting laryngeal attack.
242. The method according to embodiment 239, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) prevents the attack from progressing into a laryngeal attack.

243. The method according to any of embodiments 186 to 242, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief.

5 244. The method according to embodiment 243, wherein “symptom relief” means that the attack is rated as “a little better” or higher for two consecutive time points when assessed according to the PGI-C scale.

245. The method according to any of embodiments 186 to 244, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity.

10 246. The method according to embodiment 245, wherein “reduction in attack severity” means that the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.

15 247. The method according to any of embodiments 186 to 246, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to achieve complete attack resolution.

248. The method according to embodiment 247, wherein “complete attack resolution” means the attack severity is rated as “none” on the PGI-S scale.

Specific combination therapies

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249. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.

25 250. The method according to embodiment 249, wherein the HAE attack is characterised as “severe” according to the PGI-S scale.

251. The method according to embodiment 249, wherein the HAE attack is characterised as “very severe” according to the PGI-S scale.

30 252. The method according to any of embodiments 249 to 251, wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an abdominal attack, and a subcutaneous attack.

253. The method according to embodiment 252, wherein the HAE attack is a laryngeal attack.

254. The method according to embodiment 252, wherein the HAE attack is an attack of the neck and above.

255. The method according to embodiment 252, wherein the HAE attack is an abdominal attack.
256. The method according to embodiment 252, wherein the HAE attack is a subcutaneous attack.
- 5 257. The method according to embodiment 254, wherein the attack of the neck and above is not a laryngeal attack.
258. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: administering a plasma kallikrein inhibitor to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE, and wherein the
- 10 HAE attack is an attack of the neck and above but is not a laryngeal attack.
259. The method according to embodiment 258, wherein the HAE attack is characterised as "mild" or above according to the PGI-S scale.
260. The method according to embodiment 259, wherein the HAE attack is characterised as "mild", according to the PGI-S scale.
- 15 261. The method according to embodiment 259, wherein the HAE attack is characterised as "moderate" or above according to the PGI-S scale.
262. The method according to embodiment 261, wherein the HAE attack is characterised as "moderate", according to the PGI-S scale.
263. The method according to embodiment 261, wherein the HAE attack is characterised as
- 20 "severe" or above according to the PGI-S scale.
264. The method according to embodiment 263, wherein the HAE attack is characterised as "severe", according to the PGI-S scale.
265. The method according to embodiment 263, wherein the HAE attack is characterised as "very severe", according to the PGI-S scale.
- 25 266. The method according to any of embodiments 249 to 265, wherein the patient is aged 12 years and above.
267. The method according to embodiment 266, wherein the patient is aged between 12 and less than 18.
268. The method according to embodiment 266, wherein the patient is aged 18 years and
- 30 above.
269. The method according to any of embodiments 249 to 268, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.
270. The method according to any of embodiments 249 to 268, wherein the prophylactic
- 35 treatment is an attenuated androgen.

271. The method according to embodiment 270, wherein the attenuated androgen is selected from danazol, and oxandrolone.
272. The method according to any of embodiments 249 to 268, wherein the prophylactic treatment is tranexamic acid.
- 5 273. The method according to any of embodiments 249 to 268, wherein the prophylactic treatment is non-androgen therapy.
274. The method according to any of embodiments 249 to 268, wherein the prophylactic treatment is a C1 inhibitor.
275. The method according to any of embodiments 249 to 268, wherein the prophylactic
10 treatment is a Factor XIIa (FXIIa) inhibitor.
276. The method according to any of embodiments 249 to 268, wherein the prophylactic treatment is a plasma kallikrein inhibitor.
277. The method according to any of embodiments 249 to 268, wherein the prophylactic
15 treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
278. The method according to embodiment 277, wherein the prophylactic treatment is selected from garadacimab, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
- 20 279. The method according to embodiment 277, wherein the prophylactic treatment is Cinryze®, Haegarda®, or Berinert®.
280. The method according to embodiment 277, wherein the prophylactic treatment is selected from lanadelumab and berotralstat.
281. The method according to embodiment 280, wherein the prophylactic treatment is
25 lanadelumab.
282. The method according to embodiment 280, wherein the prophylactic treatment is berotralstat.
283. The method according to any of embodiments 249 to 282, wherein the plasma kallikrein inhibitor that is administered to the patient on-demand is sebetralstat (or a pharmaceutically
30 acceptable salt and/or solvate thereof).
284. The method according to embodiment 283, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to beginning of symptom relief.

285. The method according to embodiment 284, wherein “symptom relief” means that the attack is rated as “a little better” or higher for two consecutive time points when assessed according to the PGI-C scale.

5 286. The method according to any of embodiments 283 to 285, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to reduce the time to a reduction in attack severity.

287. The method according to embodiment 286, wherein “reduction in attack severity” means that the attack severity decreases from baseline by one or more levels on the PGI-S scale for two consecutive time points.

10 288. The method according to any of embodiments 283 to 287, wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is administered to achieve complete attack resolution.

289. The method according to embodiment 288, wherein “complete attack resolution” means the attack severity is rated as “none” on the PGI-S scale.

15 290. The method according to any of embodiments 249 to 282, wherein the plasma kallikrein inhibitor that is administered to the patient on-demand is ecallantide.

20 291. The method according to any of embodiments 257 to 290, wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) slows the progression of the attack into a laryngeal attack.

292. The method according to any of embodiments 257 to 290, wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) reduces the severity of any resulting laryngeal attack.

25 293. The method according to any of embodiments 257 to 290, wherein the HAE attack is an attack of the neck and above but is not a laryngeal attack, and wherein sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) prevents the attack from progressing into a laryngeal attack.

30 ***Drug-drug interactions***

294. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will
35 take, a concomitant dose of a strong or moderate CYP3A4 inhibitor and wherein the method

comprises reducing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

295. The method according to embodiment 294, wherein the method for treating is as described in any of the preceding embodiments.

5 296. The method according to embodiment 294 or 295, wherein the method comprises reducing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) so as to diminish the additive effect experienced when co-administered with the strong or moderate CYP3A4 inhibitor.

10 297. The method according to embodiment 296, wherein the additive effect is an increased therapeutic effect of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

298. The method according to any of embodiments 294 to 297, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 10% to about 60% of the normal dose for the patient.

15 299. The method according to embodiment 298, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 20% to about 50% of the normal dose for the patient.

300. The method according to embodiment 299, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is reduced by about 50% of the normal dose for the patient.

20 301. The method according to any of embodiments 294 to 300, wherein the normal dose for the patient is about 300mg.

302. The method according to any of embodiments 294 to 301, wherein the CYP3A4 inhibitor is a strong CYP3A4 inhibitor.

25 303. The method according to embodiment 302, wherein the strong CYP3A4 inhibitor is selected from itraconazole, ketoconazole, ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, lopinavir and ritonavir, clarithromycin, ceritinib, cobicistat, idelalisib, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, saquinavir and ritonavir, telithromycin, tipranavir and ritonavir, voriconazole, darunavir, telaprevir, stiripentol, curcumin, troleandomycin, atazanavir, naloxone, nilotinib, delavirdine, 30 loperamide, ribociclib, danoprevir, midostaurin, terfenadine, ergotamine, econazole, ditiocarb, methimazole, boceprevir, lonafarnib, amprenavir, amiodarone, and levoketoconazole.

304. The method according to embodiment 303, wherein the strong CYP3A4 inhibitor is itraconazole.

35 305. The method according to any of embodiments 294 to 301, wherein the CYP3A4 inhibitor is a moderate CYP3A4 inhibitor.

306. The method according to embodiment 305, wherein the moderate CYP3A4 inhibitor is selected from verapamil, aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, erythromycin, fluconazole, grapefruit juice, imatinib, isavuconazole, isavuconazonium, luliconazole, netupitant, miconazole, nicardipine, isoniazid, danazol, lovastatin, ziprasidone, desvenlafaxine, indalpine, zimelidine, milnacipran, fusidic acid, barnidipine, benidipine, isradipine, haloperidol, linagliptin, fosnetupitant, simeprevir, nilvadipine, primaquine, clozapine, tioconazole, venetoclax, seproxetine, fluvoxamine, fosamprenavir, cyclosporine, abiraterone, clindamycin, berotralstat, tepotinib, and lenacapavir.
307. The method according to embodiment 306, wherein the moderate CYP3A4 inhibitor is verapamil.
308. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient has taken, or will take, a concomitant dose of a strong or moderate CYP3A4 inducer and wherein the method comprises increasing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
309. The method according to embodiment 308, wherein the method for treating is as described in any of the preceding embodiments.
310. The method according to embodiment 308 or 309, wherein the method comprises increasing the normal dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) so as to compensate for the effect experienced during co-administration.
311. The method according to embodiment 310, wherein the effect experienced during co-administration is a decreased therapeutic effect of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
312. The method according to any of embodiments 308 to 311, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 10% to about 60% of the normal dose for the patient.
313. The method according to embodiment 312, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 20% to about 50% of the normal dose for the patient.
314. The method according to embodiment 313, wherein the dose of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) is increased by about 50% of the normal dose for the patient.
315. The method according to any of embodiments 308 to 314, wherein the normal dose for the patient is about 300mg.

316. The method according to any of embodiments 308 to 315, wherein the CYP3A4 inducer is a strong CYP3A4 inducer.

317. The method according to embodiment 316, wherein the strong CYP3A4 inducer is selected from 3-phenytoin, fosphenytoin, apalutamide, carbamazepine, enzalutamide, 5 ivosidenib, lumacaftor and ivacaftor, mitotane, rifampin, St. John's wort, pentobarbital, phenobarbital, enzalutamide, rimexolone, rifaximin, rifamycin, midostaurin, dexamethasone, and rifapentine.

318. The method according to embodiment 317, wherein the strong CYP3A4 inducer is 3-phenytoin.

10 319. The method according to any of embodiments 308 to 315, wherein the CYP3A4 inducer is a moderate CYP3A4 inducer.

320. The method according to embodiment 319, wherein the moderate CYP3A4 inducer is selected from efavirenz, bosentan, cenobamate, dabrafenib, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib, modafinil, nafcillin, bexarotene, avasimibe, echinacea, 15 dexamethasone, and dexamethasone acetate.

321. The method according to embodiment 320, wherein the moderate CYP3A4 inducer is efavirenz.

CLAIMS

1. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.
2. The method according to claim 1, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
3. The method according to claim 2, wherein the patient is administered a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
4. The method according to any of claims 1 to 3, wherein the patient is also being treated with a prophylactic treatment of HAE.
5. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is also being treated with a prophylactic treatment of HAE.
6. The method according to claim 5, wherein the prophylactic treatment is selected from a PKa binding agent, a bradykinin B2 receptor antagonist, a Factor XIIa (FXIIa) binding agent, or a C1INH replacement agent.
7. The method according to claim 5, wherein the prophylactic treatment is a Factor XIIa (FXIIa) inhibitor.
8. The method according to claim 5, wherein the prophylactic treatment is a plasma kallikrein inhibitor.
9. The method according to claim 5, wherein the prophylactic treatment is selected from lanadelumab, garadacimab, berotralstat, STAR 0215, C1INH replacement therapy (such as Cinryze®, Ruconest®, Berinert®, or Haegarda®), donidalorsen, and deucricitibant.
10. The method according to claims 5 to 9, wherein the patient is administered a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
11. The method according to claim 10, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose, preferably about 3 hours after the first dose.
12. A method for treating an attack of hereditary angioedema (HAE) on-demand comprising: orally administering sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) to a patient in need thereof on-demand, wherein the patient is administered a first dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof) followed by

a second dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).

13. The method according to claim 12, wherein the second dose is administered between about 2 hours and about 6 hours after the first dose.
- 5 14. The method according to claim 13, wherein the second dose is administered about 3 hours after the first dose.
15. The method according to any of claims 12 to 14, wherein the patient is administered a third dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
- 10 16. The method according to claim 15, wherein the patient is administered a fourth dose of about 300mg of sebetralstat (or a pharmaceutically acceptable salt and/or solvate thereof).
17. The method according to any of claims 5 to 16, wherein the HAE attack is characterised as “mild” or above according to the PGI-S scale.
18. The method according to any of claims 5 to 16, wherein the HAE attack is characterised as “moderate” or above according to the PGI-S scale.
- 15 19. The method according to claims 5 to 16, wherein the HAE attack is characterised as “severe” or above according to the PGI-S scale.
20. The method according to any of claims 5 to 19, wherein the first dose is administered on-demand upon recognition of a symptom of an HAE attack.
- 20 21. The method according to any of claims 5 to 20, wherein the first dose is administered on-demand within about 1 hour of recognition of a symptom of an acute HAE attack.
22. The method according to claim 21, wherein the first dose is administered on-demand within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes of the symptom of an acute HAE attack being recognised.
- 25 23. The method according to any of claims 1 to 22, wherein sebetralstat is in free base form.
24. The method according to any of claims 1 to 23, wherein the HAE attack is selected from a laryngeal attack, an attack of the neck and above, an attack of the neck and above that is not a laryngeal attack, an abdominal attack, and a subcutaneous attack.
- 30 25. The method according to claim 24, wherein the HAE attack is an attack of the neck and above that is not a laryngeal attack.