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Sebetralstat: First Oral Plasma Kallikrein Inhibitor For Acute Hereditary Angioedema

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Hereditary angioedema (HAE) is a rare, potentially life-threatening disorder caused by excessive bradykinin generation. Current injectable on-demand therapies may delay timely treatment during attacks. This review summarizes the discovery, mechanism, and clinical development of sebetralstat (KVD900), the first oral plasma kallikrein inhibitor for acute HAE. Literature from 2010–2025 was evaluated across major databases and regulatory sources, with emphasis on phase 3 KONFIDENT trial outcomes. Sebetralstat consistently reduced time to symptom relief (median 1.6–1.8 h vs 6.7 h with placebo) and demonstrated favorable tolerability with predominantly mild, transient adverse events. FDA and MHRA approvals in 2025 position sebetralstat as a patient-centered, self-administered option offering rapid, effective treatment at attack onset. Remaining needs include pediatric evaluation, real-world cost-effectiveness, and assessment of its potential role beyond acute therapy.

Keywords: Hereditary angioedema; Kallikrein inhibitor; On-demand therapy; Plasma kallikrein; Regulatory approval; Sebetralstat.

This review aligns with the journal's focus on pharmacological innovation by critically evaluating the first oral plasma kallikrein inhibitor that transforms the treatment paradigm for hereditary angioedema. Beyond its mechanistic novelty, sebetralstat exemplifies how small-molecule design can substitute for injectable biologics, improving patient autonomy and adherence. The discussion further addresses regional and translational relevance, particularly for healthcare systems in low- and middle-income countries where self-administered oral therapies can substantially reduce dependence on infusion infrastructure, enhance treatment equity, and support cost-effective rare-disease management across Asia and similar resource-limited regions.

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent, non-pitting edema of the skin, gastrointestinal tract, and upper airways. Attacks are unpredictable and can become life-threatening when the airway is involved. Unlike histamine-mediated angioedema, HAE results from excessive bradykinin formation and therefore does not respond to corticosteroids, antihistamines, or epinephrine.[1-8]

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Epidemiological studies suggest that HAE affects between 1 in 50,000 and 1 in 150,000 individuals worldwide, though underdiagnosis and misclassification likely contribute to variability in prevalence estimates. Most patients have mutations in the SERPING1 gene, which cause a deficiency or dysfunction of C1 esterase inhibitor (C1-INH). Other variants involving F12, PLG, ANGPT1, and KNG1 also contribute to HAE types with normal C1-INH levels. The disorder places a significant physical, emotional, and economic burden on patients due to the unpredictability and severity of attacks.[9-12]

Understanding the kallikrein–kinin cascade has led to targeted therapies that block bradykinin generation. Sebetralstat, the first oral plasma kallikrein inhibitor for acute HAE attacks, represents a meaningful shift away from injectable therapies. Its ease of self-administration may be especially valuable in settings with limited access to infusion facilities or trained medical staff.[13-20]

Pathophysiology of HAE

The pathophysiology of HAE is rooted in dysregulation of the kallikrein–kinin cascade. Under normal conditions, C1-INH plays a crucial role in controlling plasma kallikrein activity and regulating bradykinin formation. In patients with C1-INH deficiency or dysfunction, unchecked activation of plasma kallikrein results in excessive cleavage of high-molecular-weight kininogen into bradykinin. Bradykinin, acting via endothelial B2 receptors, increases vascular permeability and vasodilation, leading to tissue edema. This biochemical pathway explains why HAE is resistant to antihistamines and corticosteroids. The clinical phenotype corresponds directly to bradykinin-mediated vascular leakage: Cutaneous attacks: Swelling of extremities, face, or genitals, often impairing mobility or appearance. Abdominal attacks: Severe pain, vomiting, and diarrhea that mimic acute surgical conditions. Laryngeal attacks: Potentially fatal airway obstruction, historically accounting for significant mortality before effective therapies became available. Understanding this mechanistic cascade has been pivotal in identifying plasma kallikrein inhibitors such as sebetralstat, which interrupt bradykinin generation and provide a rational basis for targeted therapeutic intervention.[21-27]

Medicinal Chemistry and Mechanism of Action

Sebetralstat is an oral, selective, competitive, and reversible plasma kallikrein inhibitor. In Hereditary Angioedema (HAE), C1-INH deficiency or dysfunction leads to the uncontrolled activation of plasma kallikrein. Plasma kallikrein cleaves high-molecular-weight kininogen to generate excessive bradykinin, which causes the vascular leakage and edema characteristic of HAE attacks. Sebetralstat (KVD900) inhibits plasma kallikrein activity, thereby interrupting the generation of bradykinin and halting edema progression, leading to a reduction of angioedema attacks.[28-31] The mechanism of Action of Sebetralstat in Hereditary Angioedema is illustrated in Fig. 1.

Key pharmacokinetic attributes include

• Rapid absorption – near-complete PKa inhibition within ~15 minutes post-administration.

• Favorable oral bioavailability – facilitating immediate, self-administered dosing at symptom onset.[32-35]

This represents a major leap from parenteral therapies, aligning treatment with patient convenience.

METHODOLOGY

Search Strategy and Databases

A systematic literature search was conducted in accordance with the PRISMA 2020 guidelines to ensure comprehensive and reproducible identification of relevant studies. The following databases were searched:

• PubMed/MEDLINE
• Web of Science
• Scopus
• Google Scholar

The search strategy used combinations of keywords and Boolean operators: ("Sebetralstat" OR "KVD900" OR "EKTERLY") AND ("Hereditary Angioedema" OR "HAE") AND ("kallikrein inhibitor" OR "oral therapy" OR "on-demand treatment" OR "clinical trial" OR "FDA approval"). The reference lists of retrieved articles and review papers were also manually screened to identify any additional eligible sources.

Time Frame

The search covered literature published between January 2010 and October 2025, to include both preclinical development data and recent clinical/regulatory updates regarding sebetralstat and other plasma kallikrein inhibitors.

Inclusion Criteria

Studies were included if they met the following criteria:

1. Focused on hereditary angioedema and its on-demand or acute treatments.
2. Reported clinical, pharmacological, or mechanistic data on sebetralstat (KVD900) or related oral kallikrein inhibitors.
3. Published in peer-reviewed journals, clinical trial registries, or regulatory communications (FDA, MHRA).
4. Articles written in English and accessible in full text.

Exclusion Criteria

The following records were excluded:

• Non-English language articles.

Table 1. PRISMA 2020 flowchart

Stage	Number of Records	Description
Records identified through database search	246	PubMed (102), Web of Science (54), Scopus (47), Google Scholar (43)
Additional records identified through a manual search	18	Cross-references and regulatory documents
Records after duplicates removed	198	———
Records screened (title/abstract)	198	———-
Full-text articles assessed for eligibility	72	————
Studies included in the qualitative synthesis	35	Final dataset for review

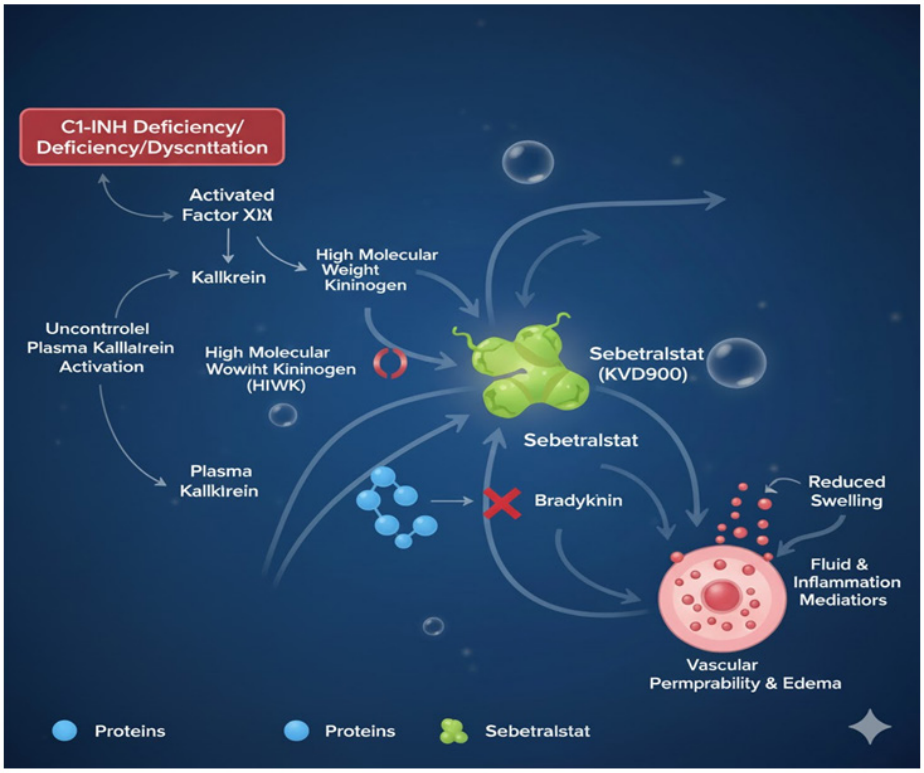

Fig. 1. Mechanism of Action of Sebetralstat in Hereditary Angioedema

• Conference abstracts without full data.
• Animal studies lacking translational significance.
• Editorials, commentaries, or press releases without verifiable primary data.

Data Extraction and Synthesis

Two independent reviewers screened titles and abstracts, retrieved full texts for eligible studies, and extracted data on trial design, population characteristics, intervention details, efficacy endpoints, and safety outcomes. Discrepancies were resolved by discussion and consensus. Quantitative synthesis was not attempted due to heterogeneity among studies; results were summarized narratively.

Bias Assessment

A formal risk-of-bias assessment was not performed in this review. Because this article is a narrative synthesis rather than a systematic review or meta-analysis, structured tools such as Cochrane RoB 2.0 or ROBINS-I were not applied. Instead, the review draws upon data from peer-reviewed clinical trials, regulatory assessments, and mechanistic studies, and the risk-of-bias evaluations provided in the original publications were considered qualitatively when interpreting the evidence.

PRISMA Flowchart

The Prism 2020 flowchart is depicted in Table 1[36-38]

The flowchart summarizes the identification, screening, eligibility, and inclusion stages of the literature selection process used in this review.

Clinical evidence

Konfident Trial (NCT05259917): Efficacy Summary

Design. Randomized, double-blind, three-way crossover trial in HAE-C1-INH (e”12 y); patients treated attacks with sebetralstat 300 mg, 600 mg, or placebo (d”2 doses/attack). Primary

Table 2. Summary of Adverse Events (All Phase 1–3 Studies)

Category	Adverse Event	Sebetralstat (300–600 mg, pooled)	Placebo	Severity / Notes
General	Headache	3.1 %	2.4 %	Mild; transient; no discontinuations
	Fatigue	2.3 %	1.7 %	Mild; self-limited
Gastrointestinal	Nausea	2.1 %	1.5 %	No vomiting or discontinuation reported
	Dyspepsia	1.8 %	1.2%	Mild; resolved spontaneously
Neurological	Dizziness	1.6%	1.4%	Mild; transient
Dermatologic / Vasomotor	Flushing	1.3%	1.0%	Transient erythema; non-serious
Musculoskeletal	Back pain / myalgia	1.1%	0.9%	No functional limitation
Serious Adverse Events (SAE)	None deemed treatment-related	——-	———	No deaths or thrombotic events reported
Laboratory / ECG Findings	No clinically meaningful trends	———-	———	Stable hematology, hepatic, and renal profiles

Table 3. Regulatory status of sebetralstat in USA & UK

Regulator	Document (primary source)	Date
FDA (CDER)	NDA Approval Letter – NDA 219301 (EKTERLY, sebetralstat)	Jul 3, 2025
FDA (label/USPI)	Full Prescribing Information (USPI)	Rev. 07/2025
FDA (listing)	Novel Drug Approvals 2025	Updated Oct 7, 2025
MHRA	MHRA Press Release (“MHRA approves sebetralstat	Jul 15, 2025
MHRA (pre-approval)	EAMS Public Assessment Report (PAR)	Mar 24, 2025

Table 4. Comparison of Key Therapies for Hereditary Angioedema (HAE)

Drug (Type)	Route of Administration	Indication	Onset of Relief	Key Advantages	Limitations
Sebetralstat (Oral plasma kallikrein inhibitor)	Oral tablet	On-demand (acute attacks)	1–2 hours	First oral on-demand option; rapid absorption; patient-friendly; no injection	Prophylaxis role not yet confirmed; limited pediatric data
Icatibant (B2 receptor antagonist)	Subcutaneous injection	On-demand (acute attacks)	~2 hours	Effective; established use	Injection-site pain; training required; cost
Berotralstat (Oral plasma kallikrein inhibitor)	Oral capsule (daily)	Long-term prophylaxis	Preventive	Convenient prophylaxis; non-invasive	Not for on-demand use; breakthrough attacks possible
Lanadelumab (Monoclonal antibody)	Subcutaneous injection (2–4 weeks)	Long-term prophylaxis	Preventive	Potent; durable prophylaxis	Injection; high cost; breakthrough attacks may occur
C1-INH replacement plasma/recombinant	IV or SC injection	On-demand & prophylaxis	30–90 minutes (IV)	Addresses underlying deficiency	IV/SC access required; cost; less convenient

endpoint: time to beginning of symptom relief (PGI-C "a little better" at e"2 consecutive time points within 12 h). Key secondary endpoints: time to reduction in severity (PGI-S) within 12 hrs. and time to complete resolution (PGI-S "none") within 24 hrs.

Primary endpoint: time to the beginning of symptom relief

• Median (IQR): 300 mg 1.61 h (0.78–7.04), 600 mg 1.79 h (1.02–3.79), placebo 6.72 h (1.34–>12). Adjusted p vs placebo: <0.0001 (300 mg) and 0.0013 (600 mg).

• Median (95% CI) (EMA analyses): 300 mg 1.69 h (1.28–2.28) vs placebo 5.57 h (2.07–NE); 600 mg 2.01 h (1.38–2.46) vs placebo 7.32 h (…). (Both significant on Gehan/stratified testing; adjusted p<0.0001 and p=0.0013, respectively.)

• Proportion reaching endpoint d"12 h: 300 mg 75.9%, 600 mg 78.9%, placebo 48–51%

Key secondary endpoints

• Time to reduction in severity d"12 h:

– Median (IQR): 300 mg 9.27 h (1.53–>12), 600 mg 7.75 h (2.19–>12), placebo >12 h (6.23–>12).

Adjusted p vs placebo: 0.004 (300 mg), 0.003 (600 mg):

– EMA table shows Gehan LS mean differences vs placebo: 300 mg "51.22 (95% CI "83.13 to "19.31), 600 mg "50.65 ("81.82 to "19.48); both significant.

Time to complete resolution d"24 h:

– Median (IQR): 300 mg >24 h (16.6–NE), 600 mg 24.0 h (10.6–NE), placebo >24 h (NE–NE).

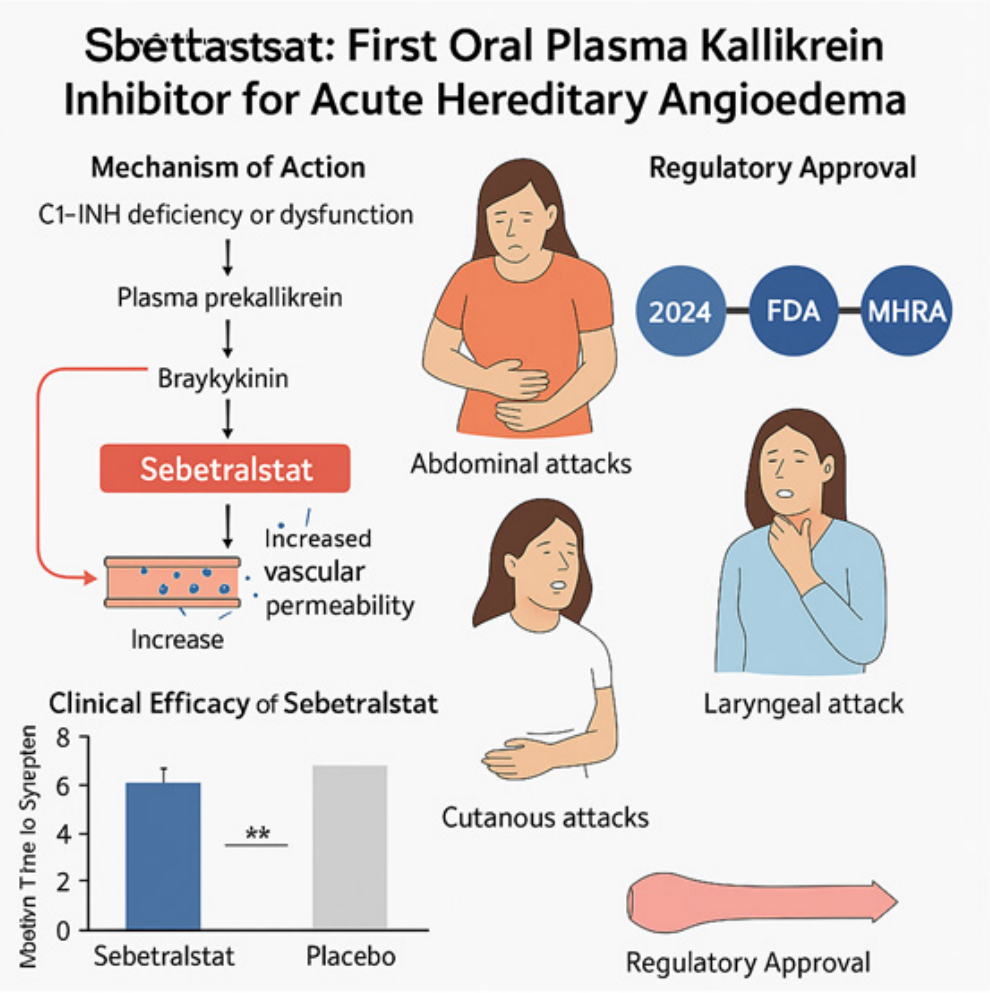

Fig. 2. Clinical & Regulatory development of Sebetralstat as the first oral plasma kallikrein inhibitor

Adjusted p vs placebo: 0.002 (300 mg), <0.001 (600 mg).

– Complete resolution d”24 h (proportion): 300 mg 42.5%, 600 mg 49.5%, placebo 27.4%

Subgroup analyses (primary endpoint; medians by subgroup)

• Baseline severity (PGI-S)—None/Mild: 300 mg 1.70 h, 600 mg 1.82 h; Moderate: 1.56 h and 2.11 h; Severe/very severe: 1.41 h and 1.51 h.

• Attack location (pooled)—Mucosal: 300 mg 1.29 h, 600 mg 1.32 h; Subcutaneous: 1.65 h and 2.12 h.

• Treatment paradigm—On-demand only: 300 mg 1.35 h, 600 mg 1.77 h; On-demand + LTP: 1.85 h and 2.03 h.

• Geography—Europe: 300 mg 1.78 h, 600 mg 1.77 h; US: 1.28 h and 1.77 h; Asia/Pacific: 1.70 h and 2.30 h.

Dose-to-dose (exploratory) comparisons

In congress supplement analyses (not powered for 600 mg vs 300 mg), hazard ratios (HR, 95% CI) for 600 mg vs 300 mg were:

• Beginning of symptom relief d”12 h HR 1.09 (0.77–1.53);

• Reduction in severity d”12 h HR 0.94 (0.62–1.43);

• Complete resolution d”24 h HR 0.80 (0.52–1.25).

Subgroup HRs by baseline severity and treatment paradigm were likewise centered near 1 with wide Cis.[39-43]

Long-Term Outcomes

Extension studies evaluating over 1,700 treated attacks confirmed the reproducibility of clinical benefit. Patients consistently experienced symptom relief within 1–1.5 hours, including those with abdominal and laryngeal attacks—sites of heightened morbidity and mortality. Importantly, real-world use revealed that patients often self-administered sebetralstat within minutes of symptom onset, supporting feasibility and practicality in routine care.[44- 45]

Safety Profile

Across all clinical trials—including the pivotal KONFIDENT Phase 3 and its long-term extension studies—sebetralstat demonstrated a consistent and favorable safety profile. No treatment-related serious adverse events (SAEs), thromboembolic events, or cardiovascular abnormalities were observed.

Adverse events (AEs) were predominantly mild to moderate, transient, and self-resolving. The overall AE incidence was comparable to placebo. No clinically relevant effects on laboratory parameters, ECG, or vital signs were detected. No QTc prolongation, hepatotoxicity, or hypersensitivity reactions were observed. Adverse events reported in Phase 1 to Phase 3 clinical trials were depicted in Table 2.[46-47]

Sebetralstat has demonstrated a favorable safety profile. Headache was the most commonly reported adverse event (~3%). Other mild, transient effects included dyspepsia, nausea, fatigue, back pain, and flushing. Importantly, no significant cardiovascular or thrombotic complications were identified during trials.[48-50]

The safety data reinforce sebetralstat’s tolerability for on-demand use in HAE. The absence of severe or cumulative toxicity, along with oral dosing convenience, underscores its suitability for early self-administration at attack onset. These findings position sebetralstat as a patient-centric alternative to injectable kallikrein inhibitors and complement long-term prophylactic regimens.

Regulatory milestones

United States (FDA).[51-53]

• **Product/Name:** EKTERLY® (sebetralstat) tablets, 300 mg.

• **Application:** NDA 219301 (new drug application).

• **Approval date:** July 3, 2025

• **Indication:** “Treatment of acute attacks of hereditary angioedema (HAE) in adult and pediatric patients aged e”12 years.”

• **Recommended dose:** 600 mg (two 300-mg tablets) at earliest recognition of an HAE attack; a second 600-mg dose e”3 h later if response is inadequate/worsening; max 1,200 mg/24 h.

• **Additional confirmation:** Listed on FDA’s Novel Drug Approvals 2025 page as “Ekterly (sebetralstat) — 07/03/2025 — To treat acute attacks of hereditary angioedema.”

United Kingdom (MHRA).[54-55]

• **Authority action:** Marketing authorization granted by MHRA.

• **Approval date:** July 15, 2025.

• **Indication & population:** “Treatment of HAE attacks in adults and adolescents aged 12 years and older.”

• **Notability:** First and only MHRA-approved oral, on-demand HAE treatment at time of decision.

• **Background (pre-licence):** Earlier EAMS scientific opinion and Public Assessment Report

(PAR) published March 24, 2025, supporting early access before full approval.

Table 3 depicts the regulatory status of sebetralstat in USA & UK.

Clinical impact and future perspectives

Clinical Impact

The approval of sebetralstat represents a major advancement in the management of HAE:

• Accessibility: Oral administration eliminates dependence on injections and infusion centers, broadening access.

• Timeliness: Rapid onset of action enables treatment at the earliest signs of an attack, reducing morbidity.

• Quality of life: Patients gain autonomy, reducing the anxiety associated with unpredictable attacks.

• Healthcare burden: Decreased emergency visits and hospitalizations are anticipated to lower overall healthcare costs.

Future Perspectives

Several avenues warrant further exploration:

1. Pediatric Development – Trials are needed to evaluate dosing, safety, and efficacy in children under 12 years.

2. Prophylactic Potential – While sebetralstat is approved for acute use, investigations into its suitability for short-term prophylaxis (e.g., perioperative settings) may broaden indications.

3. Combination Approaches – Integration with long-acting biologics or gene therapies could offer comprehensive, individualized management strategies.

4. Global Access and Equity – Ensuring affordability and availability, particularly in low-resource settings, will be critical to maximizing public health benefits.

5. Precision Medicine – Genotypic and biomarker-driven stratification may optimize patient selection and outcomes.

Overall, sebetralstat exemplifies the successful translation of molecular pathophysiology into a transformative clinical innovation, setting the stage for a new era in HAE therapy. Sebetralstat represents not only a therapeutic innovation but also a paradigm shift in rare-disease pharmacotherapy. Its oral administration aligns modern treatment with patient needs for autonomy, speed, and convenience. As further data emerge, particularly in pediatrics and prophylaxis, sebetralstat is likely to reshape standard care algorithms for HAE.[56-60]

In line with the journal's mission to advance innovative pharmacotherapy and regional applicability, this work underscores sebetralstat's role as a first-in-class oral kallikrein inhibitor offering a tangible solution to accessibility challenges in rare-disease care. The drug's molecular precision, safety, and ease of administration highlight how pharmacological innovation can bridge the gap between global discovery and regional clinical implementation, especially within emerging healthcare economies.

Cost-effectiveness and accessibility in low-resource settings

Sebetralstat may also offer advantages in terms of cost-effectiveness and accessibility, particularly in low-resource healthcare settings where infusion facilities, trained personnel, and injectable storage requirements may be limited. The oral formulation eliminates the need for specialized administration infrastructure and may reduce the frequency of emergency visits associated with delayed treatment of attacks. Although formal pharmacoeconomic analyses are still needed, the simplified delivery model has the potential to improve treatment equity, reduce indirect healthcare costs, and broaden access to timely on-demand therapy in underserved regions.

Comparison with existing on-demand therapies

A comparison with established on-demand treatments highlights how sebetralstat fits within the current therapeutic landscape. Icatibant, a bradykinin B2 receptor antagonist administered subcutaneously, provides effective symptom relief but is frequently associated with injection-site pain and requires patient training for proper use. Ecallantide, a plasma kallikrein inhibitor, must be administered in a clinical setting due to the risk of hypersensitivity reactions, which can delay treatment during an acute attack. In contrast, sebetralstat offers a non-invasive oral option with a rapid onset of relief and a favorable safety profile, facilitating timely self-administration at symptom onset. However, direct head-to-head studies are lacking, and further comparative research is needed to establish its performance relative to injectable agents across diverse clinical scenarios.

CONCLUSION

Sebetralstat has demonstrated clinically meaningful and statistically significant improvements in time to symptom relief for acute HAE attacks. In the KONFIDENT Phase 3 trial, symptom relief occurred in approximately 1.6–1.8 hours with sebetralstat compared with 6.7 hours with placebo. Most adverse events were mild and similar in frequency to placebo, supporting its suitability for on-demand use. The oral formulation provides a convenient alternative to injectable on-demand therapies. However, data remain limited to patients aged 12 years and older, and long-term or prophylactic use has not yet been established. Additional studies are needed to compare sebetralstat with existing therapies, evaluate its use in younger children, and assess its effectiveness in real-world practice.

Regulatory approvals by the FDA and MHRA in 2025 confirm the robustness of current evidence. As further data emerge, sebetralstat may play an important role in expanding access to rapid, patient-controlled treatment for HAE attacks, particularly in resource-limited settings.

Overall, current evidence supports sebetralstat as an effective and generally well-tolerated oral option for managing acute HAE attacks. Its broader clinical and pharmacoeconomic impact should be defined through longitudinal and comparative studies aligned with real-world patient outcomes.

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This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials**.**

Permission to reproduce material from other sources

Not Applicable

Author contributions

Vikrant Dandekar: Conceptualization, Methodology, Writing Original Draft; Milind Sathe: Data Collection, Analysis, Writing Review & Editing.

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