Effectiveness of Sebetralstat for the On-demand Treatment of Mucosal HAE Attacks: Interim Analysis from KONFIDENT-S

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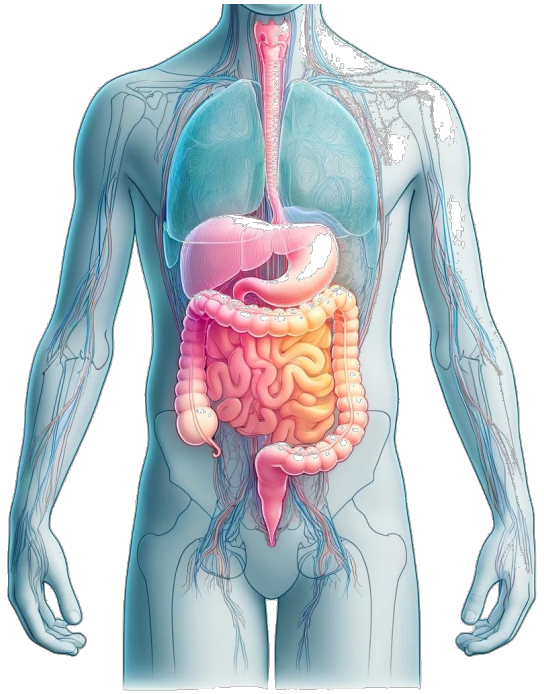
Background



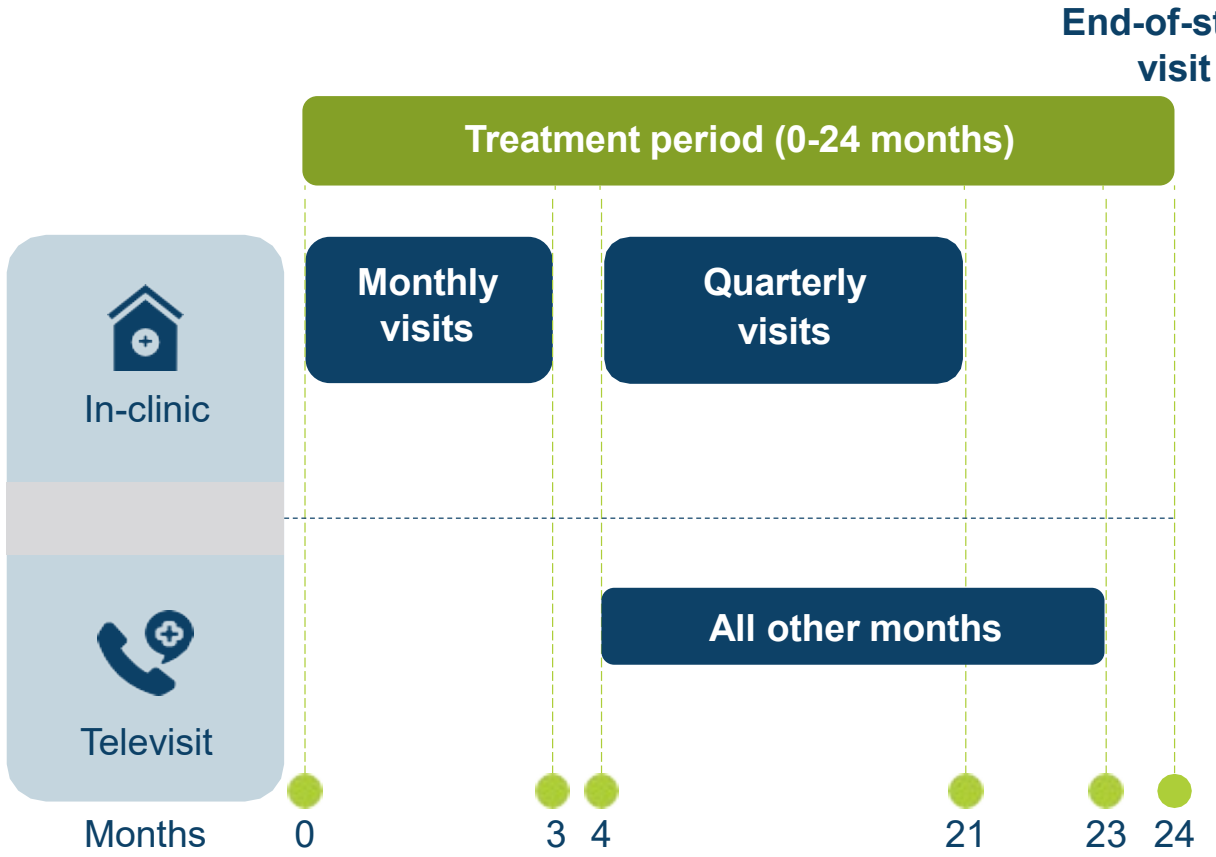
- HAE-C1INH attacks involving gastrointestinal and laryngeal tissues share an underlying pathophysiology because they affect the submucosal lining of internal surfaces[1-8]
- Mucosal attacks may progress rapidly and are associated with substantial morbidity[9,10]
  - Gastrointestinal attacks lead to severe pain, nausea, vomiting, and in some cases, may result in circulatory shock due to hypovolaemia or temporary obstruction due to the thickening of the bowel wall[9,11]
  - In the larynx, even minor oedema can rapidly progress to life-threatening airway compromise[3-5]

Here we present interim data on the safety and effectiveness of sebetralstat, an investigational oral on-demand therapy, in mucosal attacks from the ongoing 2-year open-label KONFIDENT-S study

Image generated using DALL-E. HAE-C1INH, hereditary angioedema type 1 or type 2 due to C1-inhibitor deficiency.

1. Maurer M, et al. *Allergy*. 2022;77(7):1961-1990; 2. Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3; 3. Bork K, et al. *Allergy Asthma Clin Immunol*. 2021;17(1):40; 4. De Maat S, Hofman ZLM, Maas C. *J Thromb Haemost*. 2018;16(9):1674-1685; 5. Bork K, et al. *J Emer Med*. 2016;50(4):567-580.e1; 6. Zuraw BL. *World Allergy Organ J*. 2010;3(9 Suppl):S25-S28; 7. Nzeako UC, et al. *Arch Intern Med*. 2001;161(20):2417-2429; 8. Liu D, et al. *J Inflamm Res*. 2021;13:1291-1304; 9. Bork K, et al. *Am J Gastroenterol*. 2006;101(3):619-627; 10. Bork K, et al. *J Allergy Clin Immunol*. 2012;130(3):692-7; 11. Patel N, et al. *Case Reports Immunol*. 2015;2015:925861.

KONFIDENT-S Open-label Extension Study Design



Multiple real-world elements were incorporated into the trial design, including televisits, portable multidose packs, and the elimination of a need to contact a call centre or investigator before, during, or after attacks.

Inclusion criteria:
- ≥12 years of age
- ≥2 documented HAE attacks within 3 months

Treatment:
- Participants were instructed to self-administer sebetralstat 600 mg (2 x 300-mg tablets) as early as possible after HAE attack onset
- A second administration was allowed if warranted[a]

Endpoints:
- Safety (adverse events)
- Time to beginning of symptom relief (by PGI-C)[b]
- Time to first reduction in severity (by PGI-S)[b]
- Time to complete attack resolution (by PGI-S)[c]

Study enrolled participants who had either completed the phase 3 KONFIDENT trial or were de novo, including those who participated in the phase 2 trial. For de novo participants, the enrolment visit was a screening visit.
[a]Participants were instructed to treat their attacks involving the larynx immediately with conventional on-demand therapy if the attack symptoms worsened after the initial sebetralstat administration. [b]Within 12 hours.
[c]Within 24 hours. PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.
NCT05505916, EudraCT: 2021-001176-42.

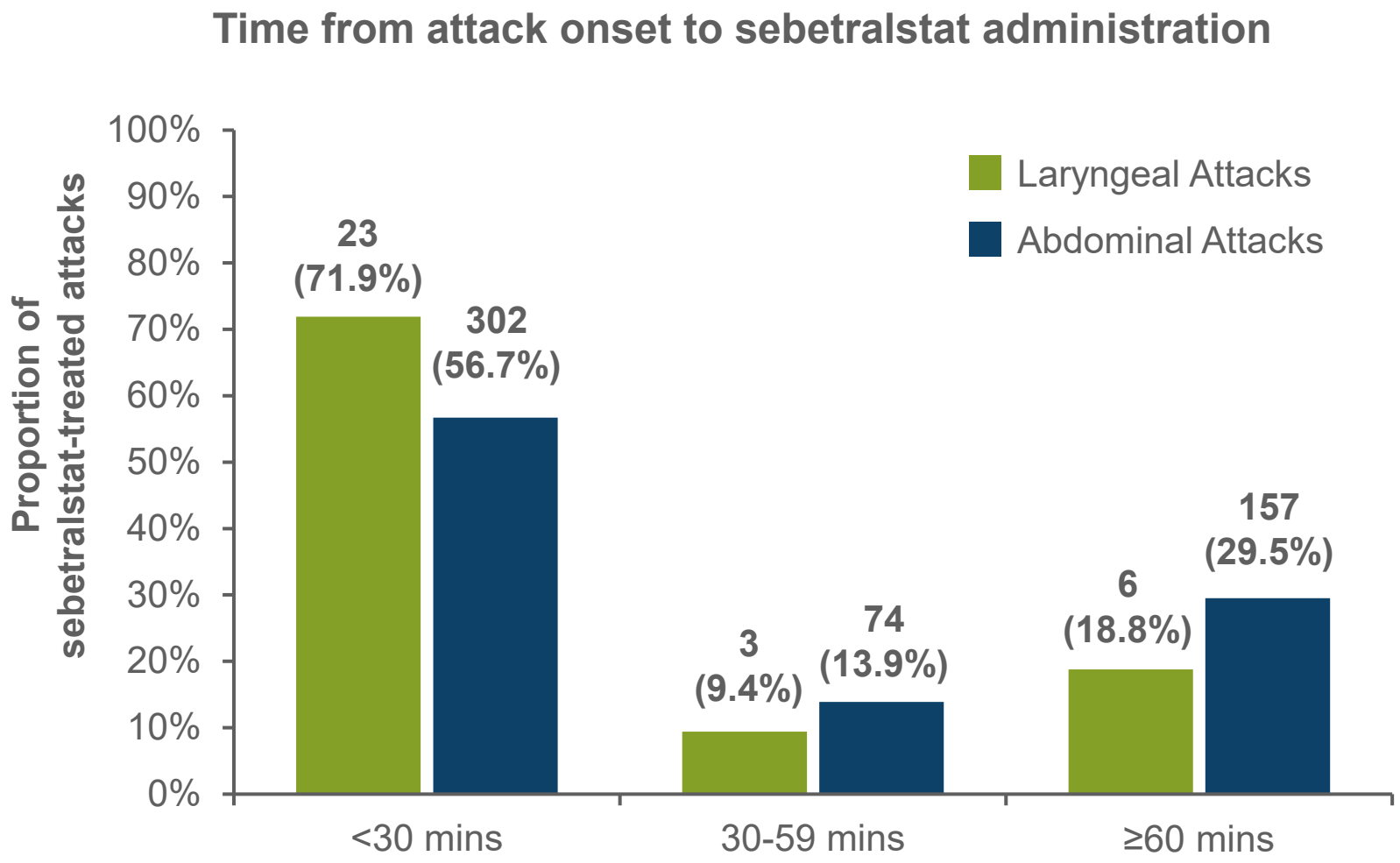
Participant Demographics and Sebetralstat-treated Attack Characteristics

	Participants Experiencing	
	Laryngeal Attacks[a] n=16	Abdominal Attacks n=102[b]
Age, mean (range), years	43.4 (15 – 67)	36.8 (12 – 77)
Age group, <18 years old, n (%)	2 (12.5)	17 (16.7)
Sex, female, n (%)	10 (62.5)	71 (69.6)
Race, n (%)		
White	13 (81.3)	76 (74.5)
Asian	2 (12.5)	13 (12.7)
Other	-	6 (5.9)
Not reported	1 (6.3)	7 (6.9)
BMI, mean (range), kg/m^2	29.66 (19.5 – 41.5)	25.92 (16.7 – 41.5)
HAE-C1INH-Type 1, n (%)	16 (100)	95 (93.1)
Current treatment regimen, n (%)		
On-demand only	9 (56.3)	77 (75.5)
On-demand + LTP	7 (43.8)	25 (24.5)
Kallikrein-inhibiting agent[e]	6 (85.7)	21 (84.0)
C1INH	1 (14.3)	4 (16.0)
Time since diagnosis, median (IQR), years	16.6 (6.1 – 25.0)	12.6 (6.0 – 22.5)

	Laryngeal Attacks n=32	Abdominal Attacks n=533
Baseline PGI-S rating, n (%)		
Mild	8 (25.0)[c]	158 (29.7)[d]
Moderate	15 (46.9)	227 (42.6)
Severe/very severe	9 (28.1)	148 (27.7)

[a]Attacks reported by participants as affecting components of the upper aerodigestive tract (ie, including larynx/throat, pharynx, and tongue oedema). [b]Of 134 participants in KONFIDENT-S. [c]PGI-S none: 1 (3.1%). [d]PGI-S none: 4 (0.8%). [e]Lanadelumab or berotralstat. BMI, body-mass index; IQR, interquartile range; LTP, long-term prophylaxis; PGI-S, Patient Global Impression of Severity.
Note: Data cutoff date of September 14, 2024.

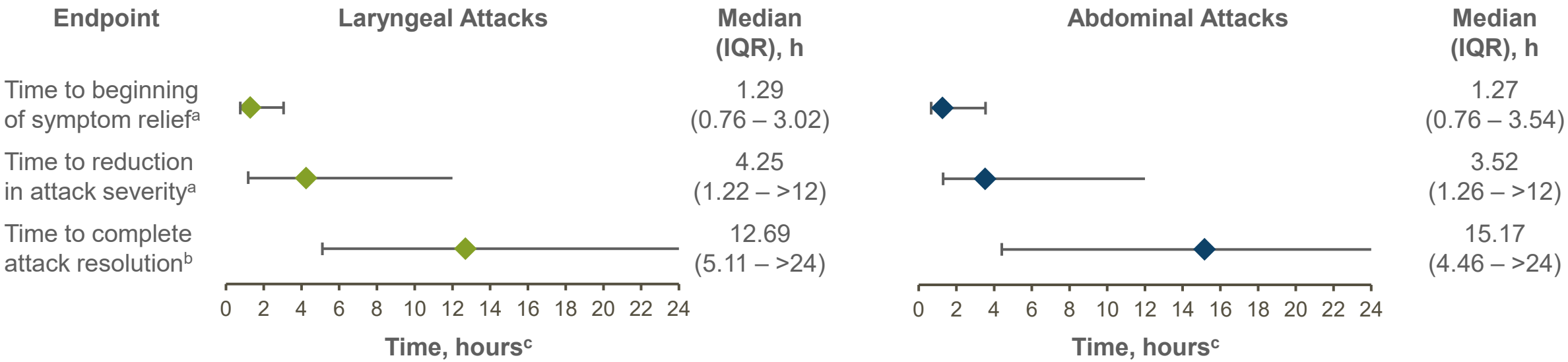
Time to Treatment



- Median (IQR) time from attack onset to sebetralstat administration was 11.5 minutes (1.0 – 34.0) for laryngeal attacks and 20.0 minutes (1.0 – 61.0) for abdominal attacks
- 81.3% of laryngeal attacks and 70.5% of abdominal attacks were treated in <1 hour of onset

IQR, interquartile range.
Note: Data cutoff date of September 14, 2024.

Effectiveness of Sebetralstat



	Laryngeal Attacks n=32	Abdominal Attacks n=533
Attacks treated with an additional dose within 12 hours, n (%)	4 (12.5)	95 (17.8)
Attacks treated with conventional treatment within 12 hours, n (%)	3 (9.4)	43 (8.1)
Proportion of attacks reaching beginning of symptom relief within 12 hours before or without an additional dose[d]	96.0%	95.8%

[a]Within 12 hours. [b]Within 24 hours. [c]Error bars display IQR. [d]Among the attacks that reached this endpoint (89.3% of laryngeal attacks; 85.7% of abdominal).
IQR, interquartile range; n, number of HAE attacks.
Note: Data cutoff date of September 14, 2024.

Safety of Sebetralstat

	Laryngeal Attacks n=16	Abdominal Attacks n=102
Any TEAE, n (%)	7 (43.8)	36 (35.3)
Treatment-related	**1 (6.3)[a]**	**6 (5.9)[a,b]**
Serious TEAE, n (%)[c]	2 (12.5)[e]	2 (2.0)
Treatment-related	**0**	**0**
Severe TEAE, n (%)[d]	3 (18.8)	2 (2.0)
Treatment-related	**0**	**0**
Any TEAE leading to permanent discontinuation, n (%)	1 (6.3)	2 (2.0)
Any TEAE leading to death, n (%)	0	0

- No participants reported difficulty swallowing sebetralstat during laryngeal or abdominal attacks

[a]Treatment-related nausea and vomiting (grade 2) occurred in the same participant, who experienced an attack involving the larynx and abdomen. [b]Treatment-related flu-like symptoms, cutaneous burning, diarrhea (3 events), headaches, myalgia (bilateral arm and bilateral leg [1 event each]; all grade 2), and vomiting (2 events, grade 1) occurred in 6 participants, who experienced an attack involving the abdomen only. [c]Serious TEAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event by medical and scientific judgement. [d]Severe (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. [e]Serious AEs resulting in hospitalisation (but considered unrelated to treatment) were 1 event of grade 3 viral meningitis occurring in 1 participant and 2 events of laryngeal HAE attack occurring in 1 participant.
AE, adverse event; n, number of participants; TEAE, treatment-emergent adverse event.
Note: Data cutoff date of September 14, 2024.

Conclusion

- Sebetralstat demonstrated similar effectiveness for laryngeal and abdominal mucosal HAE attacks
- Oral sebetralstat enabled rapid self-administration, resulting in early symptom relief and shorter attack duration in patients with HAE-C1INH
- Sebetralstat has demonstrated a favourable safety profile across multiple clinical studies and analyses, and was well-tolerated as treatment for mucosal attacks

Acknowledgements

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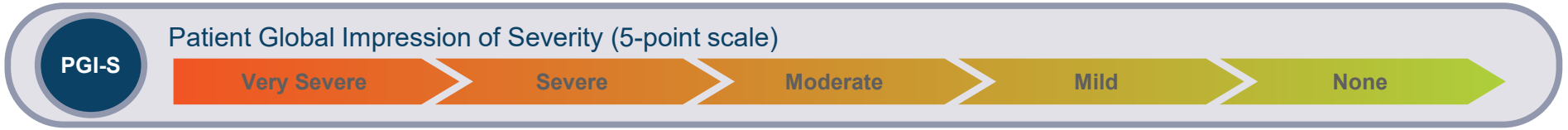
Appendix

Efficacy Endpoints

- **Primary efficacy endpoint: time to beginning of symptom relief,** defined as a rating of at least 'A Little Better' on the PGI-C scale for ≥2 consecutive time points within 12 hours

- Key secondary endpoints were tested hierarchically in the following order
  - **Time to reduction in attack severity,** defined as a decrease in PGI-S score for ≥2 consecutive time points within 12 hours
  - **Time to complete attack resolution,** defined as PGI-S rating of 'None' within 24 hours



PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Riedl M et al. *New Engl J Med*. 2024;391(1):32-43.