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Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks: Results of the Double-blind, Placebo-controlled, Phase 3 KONFIDENT Trial

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Background

- People living with hereditary angioedema (HAE), a rare genetic disease most commonly caused by deficiency or dysfunction in the C1 inhibitor (C1INH) protein (HAE-C1INH), experience unpredictable, painful, and debilitating attacks of tissue swelling that can be life-threatening if the upper airways are affected[1-3]
- Per global treatment guidelines, it is recommended that all patients with HAE-C1INH treat attacks as early as possible, consider on-demand treatment for all attacks, and always carry enough on-demand medication to treat 2 attacks[1,2]
- All currently approved therapies for on-demand treatment of HAE-C1INH attacks must be administered parenterally and are associated with delay in and/or withholding of treatment due to associated complexity[4-6]
- Sebetralstat, a plasma kallikrein inhibitor, is the first orally administered therapy being investigated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks

Objective

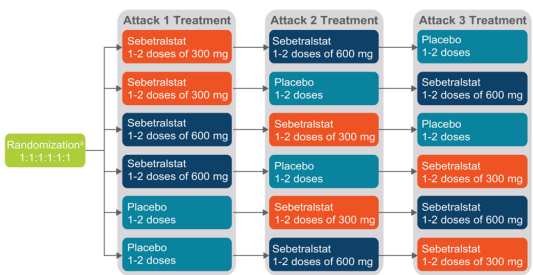
- To determine the efficacy and safety of sebetralstat 300 mg or 600 mg compared with placebo as on-demand treatment in adults and adolescents with HAE-C1INH

Methods

Study design

- The study design for KONFIDENT (NCT05259917), an international, phase 3, randomized, double-blind, placebo-controlled, 3-way crossover trial, was published previously[7]
- Adults and adolescents with a confirmed diagnosis of HAE-C1INH (type 1 or 2) and ≥2 documented HAE-C1INH attacks within 3 months were randomly assigned to 1 of 6 treatment sequences in which 3 eligible attacks were treated with sebetralstat 300 mg, 600 mg, or placebo (**Figure 1**)
  - Patients must have had access to and the ability to use conventional on-demand treatment (plasma-derived or recombinant C1INH, icatibant, ecallantide)
  - Patients receiving long-term prophylaxis (LTP) must have been on a stable dose and regimen for ≥3 months immediately before and during the trial
- Patients self-administered a single dose of sebetralstat 300 mg, 600 mg, or placebo as early as possible after recognizing the start of an attack
  - A second dose of study drug was permitted ≥3 hours after the first dose, as determined by the patient
  - Attacks in any location in the body and of any severity were eligible for treatment, except for severe laryngeal attacks, which were treated using conventional therapy

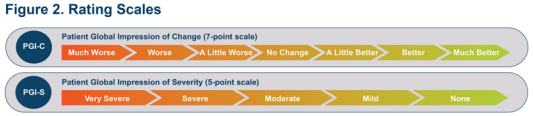
Figure 1. Study Design



[a]Stratified by treatment at enrollment (conventional on-demand treatment only versus stable LTP).

- The primary endpoint was time to beginning of symptom relief, defined as a rating of at least "A Little Better" on the Patient Global Impression of Change (PGI-C) scale for ≥2 time points in a row within 12 hours after the first dose of study drug (**Figure 2**)
- Key secondary endpoints were tested hierarchically in the following order:
  - Time to reduction in attack severity; reduction in attack severity was defined as a decrease in Patient Global Impression of Severity (PGI-S) score for ≥2 time points in a row within 12 hours after the first dose of study drug
  - Time to complete attack resolution; complete attack resolution was defined as a PGI-S rating of "None" within 24 hours after the first dose of study drug
- These endpoints were adjusted for multiplicity to assess for statistical significance (type I error rate of 0.05) for both sebetralstat doses compared with placebo

Figure 2. Rating Scales



Results

Participants and attacks

- 136 participants recruited from 66 study sites across 20 countries were randomly assigned to a treatment sequence (**Figure 3**)
- Participant demographics (**Table 1**) were similar among the 6 treatment sequences
- The Full Analysis Set included 110 participants and 264 attacks (**Table 1** and **2**)

Figure 3. Attack disposition

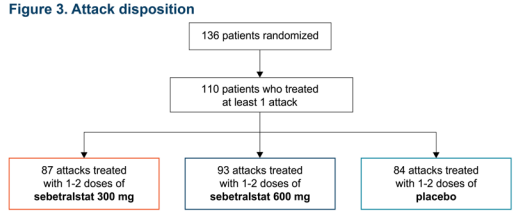


Table 1. Patient Demographics

	All patients N=110
Age, median, years (Q1, Q3)	39.5 (25.0, 49.0)
Sex, female, n (%)	66 (60.0)
Race, n (%)	
White	92 (83.6)
Asian	10 (9.1)
Black of African American	1 (0.9)
Other	1 (0.9)
Not reported	6 (5.5)
Body mass index, median, kg/m² (Q1, Q3)	26.2 (22.8, 31.7)
HAE-C1INH type, n (%)	
Type 1	101 (91.8)
Type 2	9 (8.2)
Time since HAE diagnosis, median, years (Q1, Q3)	12 (7, 22)
Current treatment regimen, n (%)	
On-demand only	86 (78.2)
LTP + on-demand	24 (21.8)

Of the 24 patients taking LTP, 11 (46%) received berotralstat, 8 (33%) received lanadelumab, and 5 (21%) received C1INH.
HAE-C1INH, hereditary angioedema with C1 inhibitor mutation; LTP, long-term prophylaxis.

Table 2. Characteristics of Treated Attacks

	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)	All attacks (n=264)
Baseline primary attack locations, n (%)[a]				
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	2 (0.8)
Baseline PGI-S category, n (%)				
None	0	0	2 (2.4)	2 (0.8)
Mild	36 (41.4)	41 (44.1)	36 (42.9)	113 (42.8)
Moderate	35 (40.2)	34 (36.6)	33 (39.3)	102 (38.6)
Severe or very severe	14 (16.1)	18 (19.4)	13 (15.5)	45 (17.0)
Number of attacks treated with a second administration, n (%)	33 (38.4)	39 (41.1)	46 (55.4)	118 (44.7)
Conventional medication use within 12 hours, n (%)	12 (13.8)	8 (8.6)	21 (25.0)	41 (15.5)
Time from onset of attack to first administration, median, minutes (Q1, Q3)	35 (6, 130)	41 (5, 142)	51 (6, 166)	41 (6, 140)
Attacks treated in <60 minutes, n (%)	53 (60.9)	50 (53.8)	44 (52.4)	147 (55.7)

[a]One attack can be characterized in several attack locations.
PGI-S, Patient Global Impression of Severity.

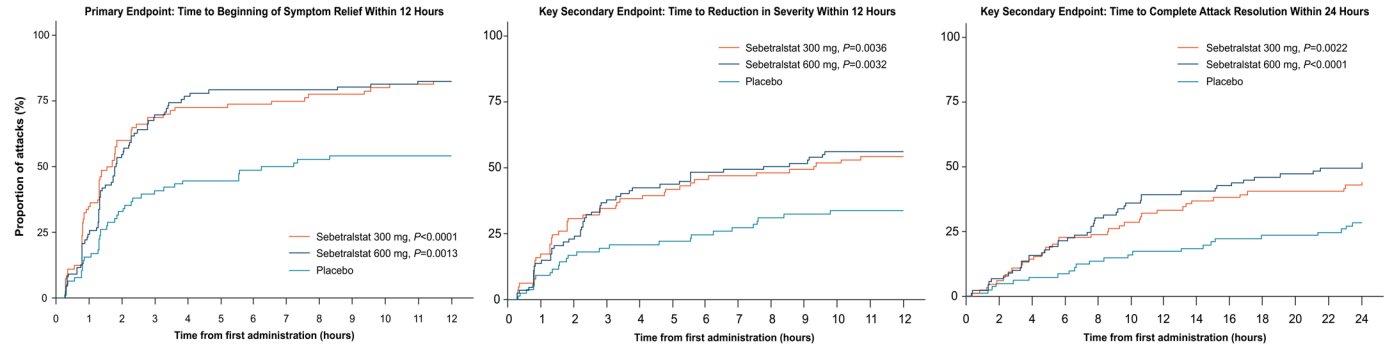
Efficacy

Table 3. Efficacy by Dosing Group

	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)
Time to beginning of symptom relief (Primary)			
P-value versus placebo	<0.0001	0.0013	--
Median time, hours (Q1, Q3)	1.61 (0.78, 7.04)	1.79 (1.02, 3.79)	6.72 (1.34, >12)
Time to reduction in attack severity (Key Secondary)			
P-value versus placebo	0.0036	0.0032	--
Median time, hours (Q1, Q3)	9.27 (1.53, >12)	7.75 (2.19, >12)	>12 (6.23, >12)
Time to complete attack resolution (Key Secondary)			
P-value versus placebo	0.0022	<0.0001	--
Median time, hours (Q1, Q3)	>24 (8.58, >24)	24.00 (7.54, >24)	>24 (22.78, >24)

- The proportions of attacks reaching beginning of symptom relief without a second dose or before a second dose was administered were 93.9% and 95.8% with sebetralstat 300 mg and 600 mg, respectively (see supplement)
- The proportions of attacks reaching reduction in severity without a second dose or before a second dose was administered were 90.9% and 95.9% with sebetralstat 300 mg and 600 mg, respectively; these proportions were 91.9% and 84.8% for complete attack resolution (see supplement)

Figure 4. Primary and Key Secondary Endpoints



Safety

- Doses of sebetralstat 300 mg and 600 mg were well-tolerated, with a safety profile comparable to that of placebo (**Table 4**)

Table 4. Safety

Number of patients, n (%)	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=93)	Placebo (n=83)
Any TEAEs	17 (19.8)	14 (15.1)	17 (20.5)
Treatment-related	**2 (2.3)**	**3 (3.2)**	**4 (4.8)**
Serious TEAEs[a]	1 (1.2)	2 (2.2)	0
Treatment-related	**0**	**0**	**0**
Severe TEAEs[b]	1 (1.2)	0	0
Treatment-related	**0**	**0**	**0**
Any TEAEs leading to permanent discontinuation	0	0	0
Any TEAEs leading to death	0	0	0

[a]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.
[b]Severe TEAE was defined as a qualitative assessment of an AE of Grade 3 severity by the investigator or as reported by the patient.
TEAE, Treatment-emergent adverse event.

Strengths and Limitations

- Strengths: KONFIDENT is the largest placebo-controlled on-demand trial conducted to date and is the most representative of the HAE population, in that it included all attack locations and levels of severity and all currently-approved non-androgen LTP agents. In addition, patients in KONFIDENT were not restricted to one administration of sebetralstat.
- Limitations: KONFIDENT was limited to 3 attacks treated and a longer safety follow-up would be informative. Although the trial was limited in racial diversity, the population of randomized patients models the population currently being treated for HAE.

Conclusions

- **The KONFIDENT trial met all primary and key secondary endpoints; beginning of symptom relief, reduction in attack severity, and complete attack resolution were significantly faster with sebetralstat 300 mg and 600 mg than with placebo**
  - **The efficacy profile was comparable between the sebetralstat 300 mg and 600 mg treatment groups**
  - **>90% of attacks that reached the primary endpoint did so without a second dose or before a second dose was administered**
- **Oral sebetralstat enabled patients to treat attacks rapidly, in line with current international treatment guidelines**
- **Up to 2 doses of sebetralstat 600 mg were well-tolerated in KONFIDENT and treatment-related adverse events were comparable with placebo**
- **Long-term safety and efficacy of sebetralstat is being studied in the KONFIDENT-S (NCT05505916) 2-year open-label extension trial**
- **In KONFIDENT, oral on-demand sebetralstat for HAE-C1INH attacks provided rapid symptom relief, reduced treatment burden, and facilitated early treatment**

Contact information

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Please visit the KalVista virtual medical booth to view this poster, as well as additional details on the methods, results, and references, after the presentation.

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Poster Supplement

Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks: Results of the Double-blind, Placebo-controlled, Phase 3 KONFIDENT Trial

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Efficacy

Supplement Table 1. Median Times to Primary and Key Secondary Endpoints by Baseline Attack Severity

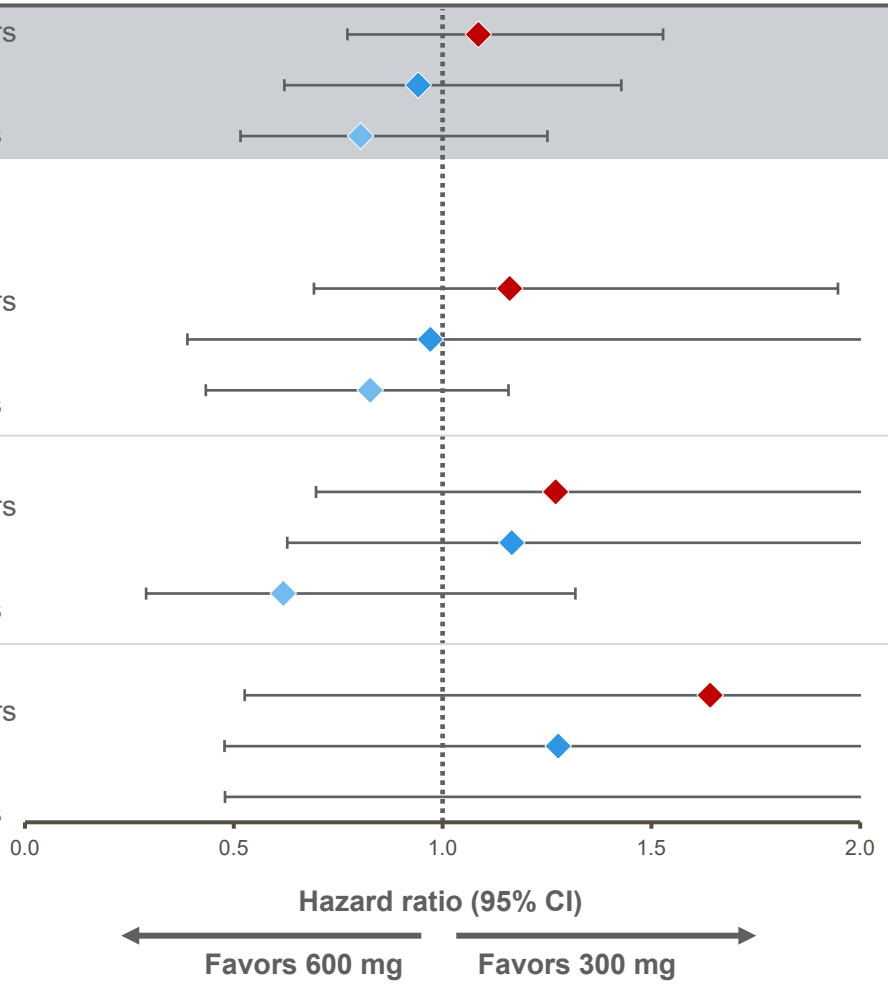
	Attacks, n			Median time, hours (Q1, Q3)	
	600 mg	300 mg		600 mg	300 mg
All attacks	93	87	Time to beginning of symptom relief within 12 hours	1.79 (1.02, 3.79)	1.61 (0.78, 7.04)
			Time to reduction in severity within 12 hours	7.75 (2.19, >12.00)	9.27 (1.53, >12.00)
			Time to complete attack resolution within 24 hours	24.00 (7.54, >24.00)	>24.00 (8.58, >24.00)
By baseline severity (PGI-S)					
None[a]/mild	41	36	Time to beginning of symptom relief within 12 hours	1.82 (1.08, 3.97)	1.70 (0.78, 3.47)
			Time to reduction in severity within 12 hours	>12.00 (9.11, >12.00)	>12.00 (8.54, >12.00)
			Time to complete attack resolution within 24 hours	18.78 (5.53, >24.00)	>24.00 (5.15, >24.00)
Moderate	34	35	Time to beginning of symptom relief within 12 hours	2.11 (1.30, 5.94)	1.56 (0.78, 7.95)
			Time to reduction in severity within 12 hours	3.27 (2.21, >12.00)	4.98 (1.14, >12.00)
			Time to complete attack resolution within 24 hours	16.80 (7.54, >24.00)	>24.00 (13.13, >24.00)
Severe/very severe	18	14	Time to beginning of symptom relief within 12 hours	1.51 (0.79, 2.98)	1.41 (0.79, 2.78)
			Time to reduction in severity within 12 hours	1.35 (0.78, 2.98)	1.31 (0.79, 2.78)
			Time to complete attack resolution within 24 hours	>24.00 (>24.00, >24.00)	>24.00 (17.05, >24.00)

- Reduction in severity was defined by a decrease of ≥1 level on the PGI-S rating scale for ≥2 time points in a row
  - For attacks rated as mild at baseline, meeting this endpoint required a decrease to “None” (ie, attack resolution)
- Complete attack resolution was defined as a PGI-S rating of “None”

[a]For 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.

Supplement Figure 1. Sebetralstat 600 mg vs 300 mg by Baseline Attack Severity

		HR (95% CI)	Attacks, n 600 mg	Attacks, n 300 mg
All attacks	Beginning of symptom relief within 12 hours	1.09 (0.77, 1.53)	93	87
	Reduction in severity within 12 hours	0.94 (0.62, 1.43)		
	Complete attack resolution within 24 hours	0.80 (0.52, 1.25)		
Attacks by baseline severity (PGI-S)				
None[a]/mild	Beginning of symptom relief within 12 hours	1.16 (0.69, 1.95)	41	36
	Reduction in severity within 12 hours	0.97 (0.39, 2.42)		
	Complete attack resolution within 24 hours	0.83 (0.43, 1.58)		
Moderate	Beginning of symptom relief within 12 hours	1.27 (0.70, 2.32)	34	35
	Reduction in severity within 12 hours	1.17 (0.63, 2.17)		
	Complete attack resolution within 24 hours	0.62 (0.29, 1.32)		
Severe/very severe	Beginning of symptom relief within 12 hours	1.64 (0.53, 5.12)	18	14
	Reduction in severity within 12 hours	1.28 (0.48, 3.41)		
	Complete attack resolution within 24 hours	2.45 (0.48, 12.57)		



[a]For 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.

Supplement Table 2. Median Times to Primary and Key Secondary Endpoints by Treatment Paradigm

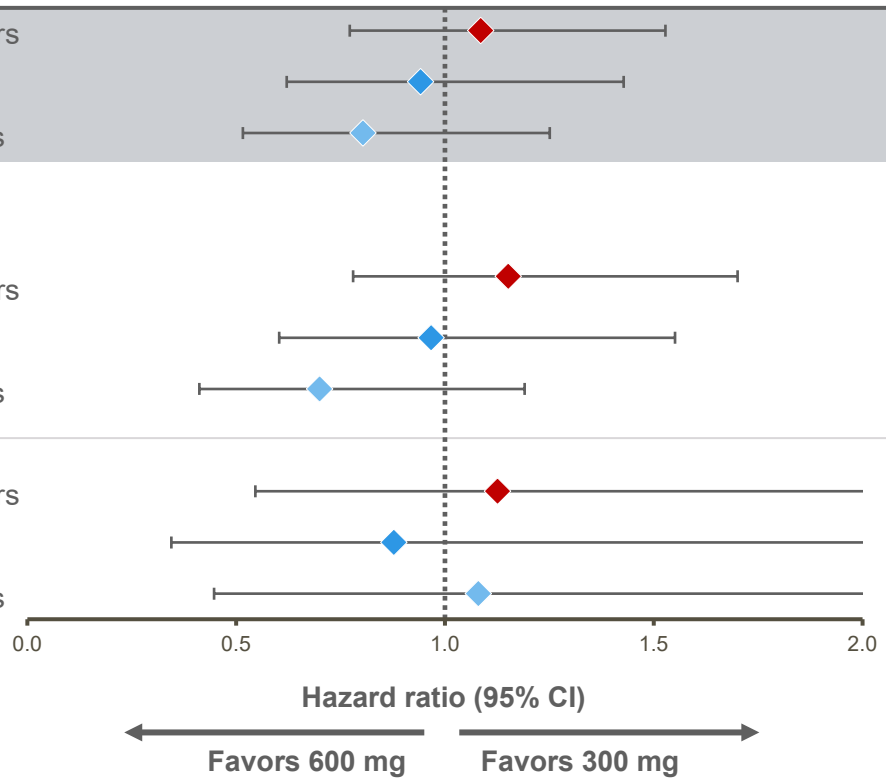
	Attacks, n			Median time, hours (Q1, Q3)	
	600 mg	300 mg		600 mg	300 mg
All attacks	93	87	Time to beginning of symptom relief within 12 hours	1.79 (1.02, 3.79)	1.61 (0.78, 7.04)
			Time to reduction in severity within 12 hours	7.75 (2.19, >12.00)	9.27 (1.53, >12.00)
			Time to complete attack resolution within 24 hours	24.00 (7.54, >24.00)	>24.00 (8.58, >24.00)
By treatment paradigm					
On-demand only	72	68	Time to beginning of symptom relief within 12 hours	1.77 (1.02, 3.79)	1.35 (0.78, 6.54)
			Time to reduction in severity within 12 hours	8.15 (2.10, >12.00)	8.45 (1.35, >12.00)
			Time to complete attack resolution within 24 hours	>24.00 (7.54, >24.00)	>24.00 (5.60, >24.00)
On-demand + LTP[a]	21	19	Time to beginning of symptom relief within 12 hours	2.03 (0.78, 3.89)	1.85 (0.79, 10.12)
			Time to reduction in severity within 12 hours	5.53 (2.27, >12.00)	9.27 (1.79, >12.00)
			Time to complete attack resolution within 24 hours	19.24 (5.28, >24.00)	17.05 (10.55, >24.00)

- Reduction in severity was defined by a decrease of ≥1 level on the PGI-S rating scale for ≥2 time points in a row
  - For attacks rated as mild at baseline, meeting this endpoint required a decrease to “None” (ie, attack resolution)
- Complete attack resolution was defined as a PGI-S rating of “None”

[a]Of the 24 participants taking LTP, 11 (46%) received berotralstat, 8 (33%) received lanadelumab, and 5 (21%) received C1INH.

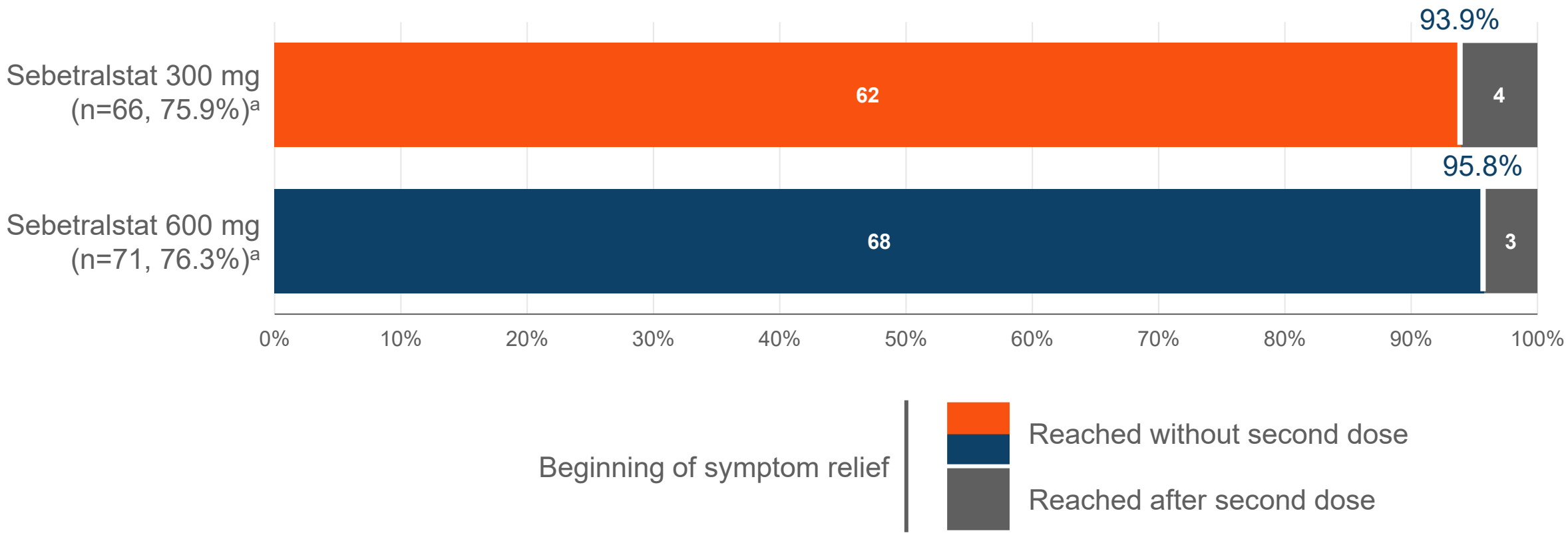
Supplement Figure 2. Sebetralstat 600 mg vs 300 mg by Treatment Paradigm

		HR (95% CI)	Attacks, n 600 mg	Attacks, n 300 mg
All attacks	Beginning of symptom relief within 12 hours	1.09 (0.77, 1.53)	93	87
	Reduction in severity within 12 hours	0.94 (0.62, 1.43)		
	Complete attack resolution within 24 hours	0.80 (0.52, 1.25)		
Attacks by treatment paradigm				
On-demand only	Beginning of symptom relief within 12 hours	1.15 (0.78, 1.70)	72	68
	Reduction in severity within 12 hours	0.97 (0.60, 1.55)		
	Complete attack resolution within 24 hours	0.70 (0.41, 1.19)		
On-demand + LTP[a]	Beginning of symptom relief within 12 hours	1.13 (0.55, 2.32)	21	19
	Reduction in severity within 12 hours	0.88 (0.35, 2.24)		
	Complete attack resolution within 24 hours	1.08 (0.45, 2.61)		



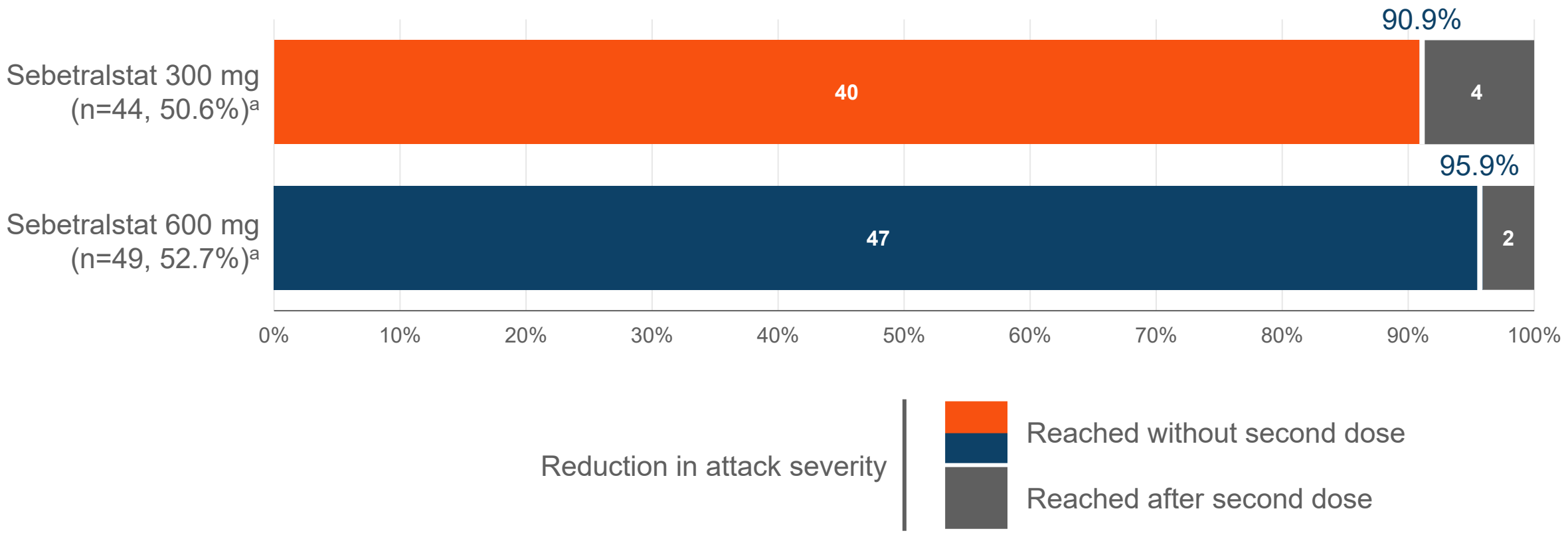
[a]Of the 24 participants taking LTP, 11 (46%) received berotralstat, 8 (33%) received lanadelumab, and 5 (21%) received C1INH.

Supplement Figure 3. Proportion of Attacks Reaching Beginning of Symptom Relief (PGI-C) With 1 vs 2 Doses



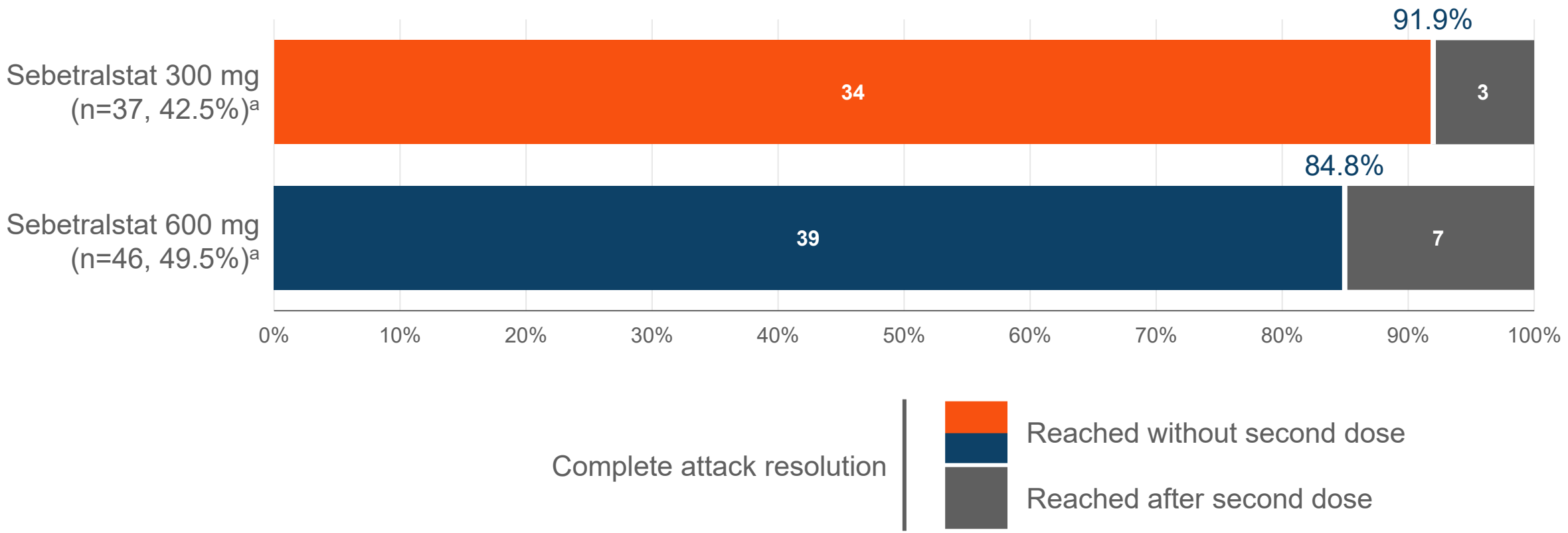
[a]Proportion of attacks reaching endpoint within 12 hours.

Supplement Figure 4. Proportion of Attacks Reaching Reduction in Attack Severity (PGI-S) With 1 vs 2 Doses



[a]Proportion of attacks reaching endpoint within 12 hours.

Supplement Figure 5. Proportion of Attacks Reaching Complete Attack Resolution (PGI-S) With 1 vs 2 Doses



[a]Proportion of attacks reaching endpoint within 24 hours.

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Safety

Supplement Table 3. Safety Summary by Number of Doses Administered

Number of patients with, n (%)	Sebetralstat				Placebo	
	300 mg (n=58)	300 mg + 300 mg (n=28)	600 mg (n=60)	600 mg + 600 mg (n=34)	1 dose (n=44)	2 doses (n=39)
Any TEAE	10 (17.2)	7 (25.0)	7 (11.7)	7 (20.6)	5 (11.4)	12 (30.8)
Treatment-related TEAE	**2 (3.4)**	**0**	**1 (1.7)**	**2 (5.9)**	**3 (6.8)**	**1 (2.6)**
Serious TEAEs[a]	1 (1.7)[b]	0	2 (3.3)	0	0	0
Treatment-related serious TEAE	**0**	**0**	**0**	**0**	**0**	**0**
Severe TEAEs[b,c]	1 (1.7)[b]	0	0	0	0	0
Treatment-related severe TEAE	**0**	**0**	**0**	**0**	**0**	**0**
Any TEAE leading to permanent discontinuation	0	0	0	0	0	0
Any TEAEs leading to death	0	0	0	0	0	0

[a]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. [b]The severe TEAE and serious TEAE listed are the same event: lumbar disc herniation that required hospitalization and was deemed severe by the investigator. [c]Severe TEAE was defined as a qualitative assessment of an AE of grade 3 severity by the investigator or as reported by the patient.
TEAE, treatment-emergent adverse event.

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Methods, References, and Acknowledgements

Supplemental Methods

- Efficacy was analyzed in the full analysis set, which was composed of all randomly assigned patients who administered study drug for ≥1 attack
- Primary and key secondary endpoints were tested using a hierarchical, fixed-sequence, closed-testing procedure based on the Bonferroni multiplicity adjustment procedure with a loop-back feature to allow 2-way alpha passing
  - Time-to-event endpoints were analyzed using Gehan score transformation test
  - Pairwise comparisons were performed for sebetralstat 300 mg versus placebo and for sebetralstat 600 mg versus placebo
- The efficacy endpoint was censored at the end of the analysis time frame by the use of conventional treatment for attacks before meeting the endpoint; the efficacy endpoint was censored at 0 hours if post-baseline data were insufficient
- The safety set consisted of all patients who received ≥1 dose of study drug

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