R083

Indirect Treatment Comparison of Oral Sebetralstat and Intravenous rhC1-INH as On-demand Treatments for Hereditary Angioedema

H. Henry Li,[1] Markus Magerl,[2,3] Timothy J. Craig,[4] Michael E. Manning,[5,6] Noemi Hummel,[7] Alice Wang,[8] Paul K. Audhya,[8] Jonathan A. Bernstein[9]

[1]Institute for Asthma and Allergy, Chevy Chase, MD, USA; [2]Angioedema Centers of Reference and Excellence (ACARE), Institute of Allergology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt–Universität zu Berlin, Berlin, Germany; [3]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [4]The Pennsylvania State University School of Medicine, Hershey, PA, USA; [5]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; [6]University of Arizona College of Medicine–Phoenix, Scottsdale, AZ, USA; [7]Certara, Lörrach, Germany; [8]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA; [9]University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, OH, USA

Background

- Hereditary angioedema (or HAE) attacks are unpredictable, and all on-demand therapies are meant to quickly stop the progression/halt the attack
- Sebetralstat, an investigational oral on-demand plasma kallikrein inhibitor, demonstrated efficacy and safety in the phase 3 randomized, placebo-controlled KONFIDENT trial, in which the primary endpoint, time to beginning of symptom relief, was measured using the Patient Global Impression of Change (PGI-C) scale[1]
- Substantial heterogeneity across hereditary angioedema (HAE) trial designs and endpoints make indirect treatment comparisons (ITCs) challenging
- This ITC was conducted to evaluate sebetralstat versus other approved therapies as an on-demand treatment for HAE attacks

Methods

SLR and ITC feasibility assessment

- A systematic literature review (SLR) was performed using National Institute for Health and Care Excellence guidelines methodology[2]; data selection adhered to Centre for Reviews and Dissemination guidelines[3] and Cochrane methodology[4]
- A feasibility assessment was conducted to determine which trials identified in the SLR met the criteria for inclusion in the ITC

ITC

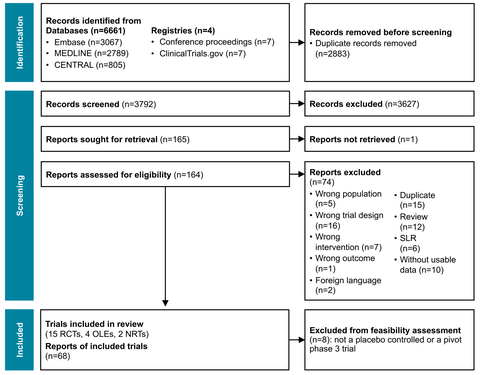
- Based on available data, Bayesian fixed-effects network meta-analyses (NMAs) were conducted to indirectly compare the efficacy and safety of oral sebetralstat 300 mg (NCT05259917)[1] and intravenous (IV) recombinant human C1 esterase inhibitor (rhC1-INH) 50 IU/kg (NCT01188564, NCT00225147, NCT00262301)[5,6]
  - For the efficacy analysis, fixed-effects NMAs with inverse variance weights were applied to obtain single hazard ratios (HRs) from two stratifications (region: US and non-US, sex: female and male)
  - Sensitivity analyses were undertaken with random-effects models
  - HRs were used for efficacy and odds ratios were used to assess safety
- A matching-adjusted indirect comparison (MAIC) was performed to adjust for differences in baseline severity and patient demographics

Results

SLR and feasibility assessment

- A total of 68 reports summarizing data from 15 randomized controlled trials, 4 open-label extensions, and 2 non-randomized trials were identified (**Figure 1**)
- The majority of trials were excluded due to differences in trial design (**Table 1**)

Figure 1. PRISMA flow diagram of reports identified in the SLR



NRT: non-randomized trial; OLE: open-label extension; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT: randomized controlled trial; SLR: systematic literature review.

Table 1. Overview of feasibility assessment

Intervention	Trial name	Primary endpoint	Primary endpoint measure	Treatment-related TEAEs reported	Primary endpoint follow-up time, hr	KM curve reported	HR reported
Sebetralstat[a,1]	KONFIDENT	Time to beginning of symptom relief	PGI-C	Yes	12	Yes	Yes
Ruconest[a,5,7]	C1-1310	Time to onset of sustained relief	TEQ	Yes	24	Yes	Yes
Ruconest[a,6]	Pooled (C1-1304-01 and C1-1205-01)	Time to beginning of symptom relief	VAS	Yes	24	Yes	Yes
Berinert[8]	IMPACT 1	Time to onset of symptom relief	Patient-directed question[b]	No	24	Yes	No
Ecallantide[9]	EDEMA3	Median TOS 4 h after dosing	TOS	No	4	Yes	No
Ecallantide[10]	EDEMA4	Change from baseline in MSCS score 4 h after dosing	MSCS	No	4	No	No
Icatibant[11]	FAST-1[c]	Median time to clinically significant relief of the index symptom	VAS-3	No	12–15	No	No
Icatibant[12]	FAST-3	Time to 50% reduction in symptom severity	VAS-3	No	12	No	No
C1-INH-nf[13]	Two RCTs	Time to onset of unequivocal symptom relief at the defining site (site of the most severe symptoms)	Symptom relief score	No	4	No	Yes[d]

[a]Trials included in the ITC. [b]No description of questions used for the outcome measure was reported in the publication. [c]The FAST-2 trial was not included because there was no placebo arm. [d]Reported as an "estimated success rate ratio."
HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; MSCS: Mean Symptom Complex Severity Score; NR: not reported; PGI-C: Patient Global Impression of Change; RCT: randomized controlled trial; TEAE: treatment-emergent adverse event; TEQ: Treatment Effect Questionnaire; TOS: Treatment Outcome Score; VAS: Visual Analog Scale; VAS-3: 3-symptom composite VAS score (mean of scores for skin swelling, skin pain, and abdominal pain).

- Only one pivotal trial reported relevant data on a comparable efficacy endpoint (time to beginning of symptom relief) for an ITC with KONFIDENT: the C1-1310 (NCT01188564) trial of IV rhC1-INH 50 IU/kg[5]
- Publications on C1-1310 and from a pooled analysis of C1-1205-01 (NCT00225147) and C1-1304-01 (NCT00262301), which also included patients treated with IV rhC1-INH 50 IU/kg,[6] reported comparable safety outcomes to enable ITCs with sebetralstat[1]
- There were several differences between trial designs, including the following:
  - In KONFIDENT, patients with any attack severity were instructed to self-administer oral sebetralstat as early as possible after attack onset, whereas patients in the IV rhC1-INH trials were required to report to the clinic within 5 hours of attack onset once an attack progressed to a Visual Analog Scale (0-100 mm) score of ≥50 mm[1,5,6]
  - Time to beginning of symptom relief was measured using the PGI-C scale[14] within 12 hours of attack onset in KONFIDENT and the Treatment Effect Questionnaire (TEQ), which used similar questions as the PGI-C, within 24 hours of attack onset in C1-1310[1,5]

Table 2. Baseline characteristics of patients in the clinical trials included in the ITCs[a]

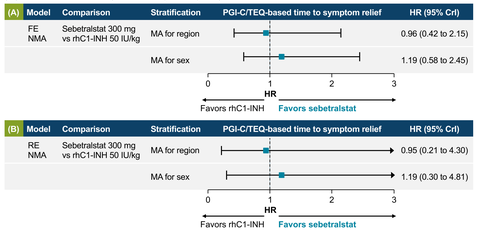
	KONFIDENT[1]		C1-1310[5]		C1-1205-01/C1-3401-01[6]		
	Oral sebetralstat 300 mg (n=87)	Oral placebo (n=84)	IV rhC1-INH 50 IU/kg (n=44)	IV placebo (n=31)	IV rhC1-INH 50 IU/kg (n=12)[b]	IV placebo (n=13)[b]	IV placebo (n=16)[c]
White, n (%)	73 (84)	73 (87)	42 (95)	30 (97)	12 (100)	11 (85)	16 (100)
Female, n (%)	54 (62)	55 (65)	28 (64)	19 (61)	8 (67)	12 (92)	9 (56)
Age, y							
Mean (SD)	NR	NR	39.4 (12.59)	41.4 (15.38)	40.7 (12.2)	32.4 (11.3)	44.5 (16.8)
Median (IQR)	37.0 (25.0–49.0)	38.0 (25.0–49.0)	NR	NR	NR	NR	NR
Use of prophylactic treatment, n (%)	19 (21)	18 (22)	22 (50)	15 (48)	NR	NR	NR
Baseline severity, n (%)							
None	0	2 (2)	—	—	—	—	—
Mild	36 (41)	36 (43)	—	—	—	—	—
Moderate	35 (40)	33 (39)	—	—	—	—	—
Severe	12 (14)	10 (12)	44 (100)[d]	31 (100)[e]	12 (100)[f]	31 (100)[g]	16 (100)[g]
Very severe	2 (2)	3 (4)	—	—	—	—	—
Missing	2 (2)	0	—	—	—	—	—

[a]KONFIDENT and C1-1310 were included in the ITC of efficacy (time to beginning of symptom relief). Data from KONFIDENT, C1-1310, and a pooled analysis of C1-1205-01 and C1-3401-01 were included in the ITC of safety (incidence of treatment-related treatment-emergent adverse events). [b]Data from C1-1205-01. [c]Data from C1-3401-01. [d]Mean (range) VAS score at BL for primary attack site was 73.5 mm (50–100 mm). [e]Mean (range) VAS score at BL for primary attack site was 77.3 mm (49–100 mm). [f]Mean (range) VAS score at BL for most serious site was 77.6 mm (51–100 mm). [g]Combined Mean (range) VAS score at BL for most serious site in placebo arm was 80.2 mm (49–100 mm).
BL, baseline; IQR: interquartile range; ITC: indirect treatment comparison; IV: intravenous; NR: not reported; rhC1-INH: recombinant human C1 esterase inhibitor; SD: standard deviation; VAS: visual analog scale.

NMA: Efficacy

- The fixed-effects NMA model found no significant difference in the time to beginning of symptom relief between oral sebetralstat and IV rhC1-INH (**Figure 2A**)
- The sensitivity analyses yielded consistent results (**Figure 2B**)

Figure 2. Time to beginning of symptom relief per (A) fixed-effects (base case) and (B) random-effects (sensitivity analysis) models

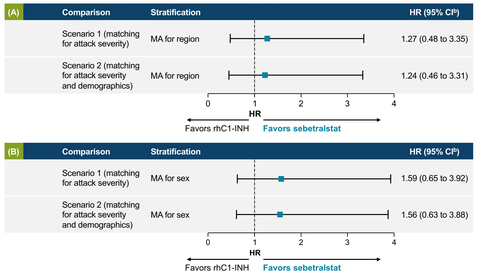


HR values >1 favor oral sebetralstat over IV rhC1-INH.
In KONFIDENT, time to beginning of symptom relief was defined as a rating of at least "A Little Better" at ≥2 consecutive time points within 12 hours per the PGI-C scale, and in the rhC1-INH trial time to onset of sustained relief was defined as a rating of "A Little Better," "Better," or "Much Better", decrease in the intensity of attack symptoms, and persistence of improvement at the next assessment with 24-hour follow-up per the TEQ.
CrI: credible interval; FE: fixed effects; HR: hazard ratio; IV: intravenous; MA: meta-analysis; NMA: network meta-analysis; PGI-C: Patient Global Impression of Change; RE: random effects; rhC1-INH: recombinant human C1 esterase inhibitor; TEQ: Treatment Effect Questionnaire.

MAIC: Efficacy

- No significant difference in the time to beginning of symptom relief between oral sebetralstat and IV rhC1-INH was found after MAIC
  - After matching for baseline attack severity, the time to beginning of symptom relief numerically favored oral sebetralstat over IV rhC1-INH based on meta-analyses of hazard ratios for region and sex (**Figure 3A**)
  - After matching for baseline attack severity and patient demographics (age, sex, and race), the results did not appreciably change (**Figure 3B**)

Figure 3. Time to beginning of symptom relief matched for (A) baseline attack severity[a] only and (B) baseline attack severity,[a] age, sex, and race

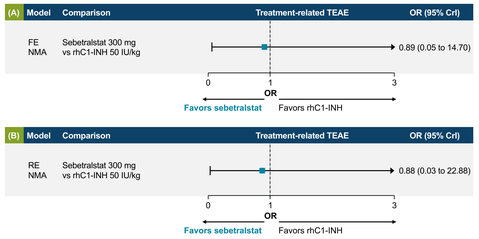


[a]Baseline attack severity was defined as the maximum of 3 baseline overall severity VAS scores. [b]HR values >1 favor oral sebetralstat over IV rhC1-INH.
CI: confidence interval; HR: hazard ratio; IV: intravenous; MA: meta-analysis; MAIC: matching-adjusted indirect comparison; rhC1-INH: recombinant human C1 esterase inhibitor; VAS: Visual Analog Scale.

NMA: Safety

- The fixed-effects NMA model found no significant differences of treatment-related treatment-emergent adverse events (TEAEs) (**Figure 4**)
  - Injection site reactions were not included in the published literature

Figure 4. Treatment-related TEAEs per (A) fixed-effects (base case) and (B) random-effects (sensitivity analysis) models



OR values <1 favor oral sebetralstat over IV rhC1-INH.
CrI: credible interval; FE: fixed effects; IV: intravenous; NMA: network meta-analysis; OR: odds ratio; RE: random effects; rhC1-INH: recombinant human C1 esterase inhibitor; TEAE: treatment-emergent adverse event.

Limitations

- Despite the careful feasibility assessment, several differences noted in this ITC between the designs of the trials may have affected these results

Conclusions

- **Despite differences in routes of administration, mechanisms of action, and trial designs, this ITC found no significant differences in either efficacy between oral sebetralstat and IV rhC1-INH for the on-demand treatment of attacks**
- **There were no apparent differences in safety between oral sebetralstat and IV rhC1-INH (excluding injection site reactions)**

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Disclosures

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