Systematic Literature Review of Recombinant Human C1 Esterase Inhibitor (rhC1-INH) and Other Products for the On-Demand Treatment of Hereditary Angioedema Attacks

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Shifts in trial design and setting complicate cross-trial comparisons

Differences in populations, attack characteristics, prophylaxis use, end point definitions, redosing, rescue therapy, and censoring may alter observed treatment effect

Valid indirect treatment comparisons require end point alignment and adjustment for population differences

BACKGROUND

- HAE is a rare genetic disorder affecting approximately 1 in 50,000 people[1]
- Patients with HAE experience recurrent, unpredictable swelling (attacks) affecting various areas, often causing considerable morbidity and impacting QOL[1-5]
- On-demand products to treat HAE attacks include Berinert® (C1 esterase inhibitor, human), Firazyr® (icatibant), Kalbitor® (ecallantide), RUCONEST® (C1 esterase inhibitor [recombinant]), and sebetralstat (KVD900)

OBJECTIVE

- Through an SLR, this study sought to better understand clinical trial designs, populations, and outcomes for on-demand HAE treatments

METHODS

- A systematic literature search (Table 1) was executed and included:
  - Electronic database searches in MEDLINE and MEDLINE In-Process, Embase, and The Cochrane Library (search dates: inception to October 2024)
  - Hand searches of reviewed of bibliographies of published systematic reviews and meta-analyses as well as ClinicalTrials.gov, accessdata.fda.gov, journal sites, and corporate websites containing relevant publications
  - Grey literature searches of AAAAI, EAACI, and ACAAI (search dates: 2022 to 2024)
- Two independent reviewers completed trial selection and data extraction; discrepancies were resolved by a third independent reviewer

TABLE 1 PICOS-T Criteria

CATEGORY	INCLUSION CRITERIA	EXCLUSION CRITERIA
POPULATION	• Patients with HAE (acute attacks)	• Healthy volunteers
INTERVENTIONS	• RUCONEST • Berinert • Kalbitor • Firazyr • Sebetralstat	• Interventions other than those listed in the inclusion criteria • Prophylactic use of an intervention of interest
COMPARATORS	• Placebo • Best supportive care • Any of the above listed interventions	• Any nonpharmacologic interventions • Comparators other than those listed in the inclusion criteria
OUTCOMES	• Efficacy outcome(s) as measured in the study • Safety outcomes: AEs, SAEs	• Trials not reporting outcomes listed in the inclusion criteria
STUDY DESIGN	• Phase 2-4 RCTs (including their OLE studies) • SLRs, meta-analyses, or NMAs of relevant RCTs	Any other study designs, including: • Observational studies • Case studies/case reports • Economic evaluations • Editorials, notes, comments, or letters • Narrative or nonsystematic literature reviews • Nonhuman studies • Pharmacokinetic or pharmacodynamic studies • Phase 1 RCTs
TIME LIMIT	• Database inception to Oct 2024 (articles) • 2022 to Oct 2024 (conference abstracts)	• Full text not retrievable • Conference abstracts published before 2022
LANGUAGE	English	
COUNTRIES	No restriction on geography	

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RESULTS

- A total of 22 unique studies (12 RCTs and 10 OLEs) were reported in 101 publications (Figure S1)

TABLE 2 Trial Design and Attack Criteria Vary Among Trials

NR Data are not reported, missing, or could not be found

		STUDY DESIGN		ATTACK ELIGIBILITY CRITERIA	
IMP	TRIAL	DESIGN	SITE	TIME FROM ATTACK ONSET	SEVERITY REQUIREMENT
Berinert	IMPACT-1	Parallel	Center	<5 h	NR
Kalbitor	EDEMA-1	NR	Center	NR	NR
	EDEMA-3	Parallel	Center	<8 h	TOS >0
	EDEMA-4	Parallel	Center	<8 h	MSCS >0
Firazyr	FAST-1	Parallel	Center	<6 h	VAS ≥30 mm
	FAST-2	Parallel	Center	<6 h	VAS ≥30 mm
	FAST-3	Parallel	Center	<6 h	VAS ≥30 mm
RUCONEST	C1 1304	Parallel	Center	<5 h	VAS ≥50 mm
	C1 1205	Parallel	Center	<5 h	VAS ≥50 mm
	C1 1310	Parallel	Center	<5 h	VAS ≥50 mm
Sebetralstat	KVD900-201	Crossover	Center	NR	PGI-S < severe
	KONFIDENT	Crossover	Home	Treat immediately	No criteria

STUDY DESIGN

- Among trials reporting design (Table 2), 9 used parallel and 2 used crossover assignment
- 11 of 12 trials were center-based; 1 was home-based with e-diary data collection

ATTACK RECRUITMENT

- After attack onset, 9 center-based trials required presentation to study site within 5 to 8 hours, whereas the home-based trial instructed immediate treatment (Table 2)
- Only Firazyr and RUCONEST trials adjudicated attacks by requiring a minimum VAS score ≥30 mm or ≥50 mm, respectively, without signs of regression

TABLE 3 High Variability in Baseline Attack and Treatment Characteristics Limit Between-Study Comparisons

NR Data are not reported, missing, or could not be found; % Graphical representation of the percentage

				ATTACK LOCATIONS			BASELINE ATTACK SEVERITY				TREATMENT REGIMEN AND TIMING	
IMP	TRIAL	IMP	PT/ATTACK, COUNT	ABDOMINAL, n (%)	PERIPHERAL, n (%)	ABOVE THE NECK, n (%)	BASELINE VAS, MEAN (SD)	MILD, n (%)	MODERATE, n (%)	SEVERE, n (%)	VERY SEVERE, n (%)	LTP USE, n (%)	TIME TO TREAT, MEDIAN (IQR), MIN
Berinert	IMPACT-1	C1-INH 10 IU/kg	39	31 (79.5)	NR	8 (20.5)[a]	NR	NR	32 (82.1)	7 (17.9)	NR	NR	NR
		C1-INH 20 IU/kg	43	34 (79.1)	NR	9 (20.9)[a]	NR	NR	27 (62.8)	16 (37.2)	NR	NR	NR
		Placebo	42	33 (78.6)	NR	8 (19.0)[a]	NR	NR	26 (61.9)	16 (38.1)	NR	NR	NR
Kalbitor	EDEMA-3	Ecallantide 30 mg	36	20 (55.6)[b]	25 (69.4)[b,c]	4 (11.1)[b]	NR	NR	NR	NR	NR	NR	NR
		Placebo	36	21 (58.3)[b]	21 (58.3)[b,c]	9 (25.0)[b]	NR	NR	NR	NR	NR	NR	NR
	EDEMA-4	Ecallantide 30 mg	48	18 (37.5)[b]	34 (70.8)[b,d]	22 (45.8)[b,e]	NR	NR	NR	NR	NR	NR	NR
		Placebo	48	27 (56.3)[b]	21 (43.8)[b,d]	22 (45.8)[b,e]	NR	NR	NR	NR	NR	NR	NR
Firazyr	FAST-1	Icatibant 30 mg	27	13 (48.1)	14 (51.9)[d]	NR	69.3 (NR)	NR	NR	NR	NR	NR	456 (NR)
		Placebo	29	16 (55.2)	13 (44.8)[d]	NR	67.7 (NR)	NR	NR	NR	NR	NR	600 (NR)
	FAST-2	Icatibant 30 mg	36	12 (33.3)	24 (66.7)[d]	NR	63.7 (NR)	NR	NR	NR	NR	NR	630 (NR)
		Tranexamic acid	38	15 (39.5)	23 (60.5)[d]	NR	61.5 (NR)	NR	NR	NR	NR	NR	414 (NR)
	FAST-3	Icatibant 30 mg	43	17 (39.5)	26 (60.5)[d]	NR	NR	NR	NR	NR	NR	NR	390 (NR)
		Placebo	45	19 (42.2)	26 (57.8)[d]	NR	NR	NR	NR	NR	NR	NR	330 (NR)
RUCONEST	C1 1304	rhC1-INH 100 U/kg	16	7 (43.8)	9 (56.3)	2 (12.5)[f]	76.3 (17.4)	NR	NR	NR	NR	8 (50.0)	215 (186-268)
		Placebo	16	6 (37.5)	8 (50.0)	4 (25.0)[f]	78.5 (12.1)	NR	NR	NR	NR	13 (81.0)	235 (195-310)
	C1 1205	rhC1-INH 100 U/kg	13	5 (38.5)	6 (46.2)	2 (15.4)[f]	82.5 (12.5)	NR	NR	NR	NR	NR	317 (245-389)
		rhC1-INH 50 U/kg	12[g]	5 (41.7)	6 (50.0)	0[f]	77.6 (14.4)	NR	NR	NR	NR	NR	347 (299-788)
		Placebo	13	3 (23.1)	3 (23.1)	6 (46.2)[f]	82.3 (17.2)	NR	NR	NR	NR	NR	315 (285-370)
	C1 1310	rhC1-INH 50 U/kg	44	16 (36.4)	19 (43.2)	8 (18.2)[h]	73.5 (14.3)	NR	NR	NR	NR	22 (50.0)	235 (180-280)
		Placebo	31	12 (38.7)	14 (45.2)	5 (16.1)[h]	77.3 (12.6)	NR	NR	NR	NR	15 (48.0)	261 (212-312)
Sebetralstat	KVD900-201	Sequence 1	58	16 (27.6)	40 (69.0)	NR	NR	26 (44.8)	28 (48.3)	1 (1.7)	1 (1.7)	NR	NR
		Sequence 2	55	14 (25.5)	37 (67.3)	NR	NR	31 (56.4)	23 (41.8)	0	1 (1.8)	NR	NR
	KONFIDENT	Sebetralstat 300 mg	87	35 (40.2)[b]	56 (64.4)[b,i]	11 (12.6)[b,i]	NR	36 (41.4)[k]	35 (40.2)[k]	12 (13.8)[k]	2 (2.3)[k]	19 (21.8)	35 (6-130)
		Sebetralstat 600 mg	93	42 (45.2)[b]	54 (58.1)[b,i]	13 (14.0)[b,i]	NR	41 (44.1)[k]	34 (36.6)[k]	16 (17.2)[k]	2 (2.2)[k]	21 (22.6)	41 (5-142)
		Placebo	84	37 (44.0)[b]	43 (51.2)[b,i]	13 (15.5)[b,i]	NR	36 (42.9)[k]	33 (39.3)[k]	10 (11.9)[k]	3 (3.6)[k]	18 (21.4)	51 (6-166)

[a]One patient in the IMPACT-1 study was originally randomized with a facial attack, which was later reassessed as a laryngeal attack. The treatment group of this patient was not specified. [b]An attack may be reported in more than one location. [c]This includes attacks in the genital or buttocks, external head or neck, or cutaneous locations. [d]Reported as cutaneous attack locations. [e]This includes attacks classified as occurring in the oropharyngeal head/neck and nonoropharyngeal head and neck locations. [f]This includes attacks classified as occurring in the OPPL location. [g]The sample size of the ITT population of the rhC1-INH 50 U/kg arm in C1 1205 is 13, but only 12 patients were evaluated. [h]This includes attacks classified as occurring in the facial or oropharyngeal-laryngeal locations. [i]This includes attacks in the arms, hands, legs, feet, or torso. [j]This includes attacks classified as occurring in the head, face, neck, larynx, or throat. [k]The severity of attack was determined using the PGI-S (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe).

PATIENT TREATMENT REGIMEN AND TIMING

- **Prophylaxis**: In C1 1304, C1 1310, and KONFIDENT trials, 50%, 50%, and 21.8% to 22.6% of patients received prophylaxis in IMP arms, respectively (Table 3)
- **Time to treat:** The KONFIDENT trial was conducted in the home setting, and patients were instructed to treat immediately, which may have led to the substantially faster treatment times (median, 35-51 min). The remaining trials were conducted in treatment centers with time to treat ranging from 215-630 minutes

ATTACK LOCATIONS AND BASELINE SEVERITY

- **Attack locations**: Locations varied substantially among trials, with abdominal attacks ranging from 23.1% to 79.5% and peripheral attacks from 23.1%-70.8%. Multiple locations per attack were reported in EDEMA and KONFIDENT trials, whereas others reported either the primary or most severe location (Table 3)
- **Attack severity**: All attacks in IMPACT-1 were moderate (68.5%) or severe (31.5%), whereas most patients in KONFIDENT experienced mild (42.8%) to moderate (38.6%). Mean VAS scores for RUCONEST trials ranged from 73.5 to 82.5, indicating patients had more severe attacks at baseline compared with Firazyr (61.5-69.3)

TABLE 4 Redosing, Rescue Therapy, and Censoring Are Inconsistent Among Trials

NR Data are not reported, missing, or could not be found; % Graphical representation of the percentage

				REDOSING AND RESCUE BY IMP					CENSORING DETAIL BY IMP				
IMP	TRIAL	INTERVENTION	PT/ATTACK, COUNT	REDOSE ALLOWED?	RESCUE ALLOWED?[a]	REDOSE GIVEN	REDOSE, n (%)	RESCUE, n (%)	END POINT CUTOFF	RESCUE	REDOSE	LOST OR END OF FOLLOW-UP	CENSORED,[b] n (%)
Berinert	IMPACT-1	C1-INH 10 IU/kg	39			C1-INH 10 IU/kg	13 (33.3)	NR					NR
		C1-INH 20 IU/kg	43	Yes	Yes	Placebo	8 (18.6)	NR	No	Yes	Yes	Yes	13 (30.2)
		Placebo	42			C1-INH 20 IU/kg	24 (57.1)	NR					23 (54.8)
Kalbitor	EDEMA-3	Ecallantide 30 mg	36	Yes	Yes	Ecallantide 30 mg	2 (5.6)	5 (13.9)	Yes	NR	Yes	Yes	NR
		Placebo	36			Ecallantide 30 mg	1 (2.8)	13 (36.1)					NR
	EDEMA-4	Ecallantide 30 mg	48	Yes	Yes	Ecallantide 30 mg	15 (31.2)	16 (33.3)	Yes	NR	Yes	Yes	1 (2.1)
		Placebo	48			Ecallantide 30 mg	22 (45.8)	24 (50)					6 (12.5)
Firazyr	FAST-1	Icatibant 30 mg	27	No	Yes	NR	NR	6 (22)	No	No	No	Yes	1 (3.7)
		Placebo	29			NR	NR	14 (48)					1 (3.4)
	FAST-2	Icatibant 30 mg	36	No	Yes	NR	NR	7 (19)	No	No	No	Yes	0
		Tranexamic acid	38			NR	NR	12 (32)					2 (5.3)
	FAST-3	Icatibant 30 mg	43	No	Yes	NR	NR	3 (7.0)	No	No	No	Yes	0
		Placebo	45			NR	NR	18 (40)					3 (6.7)
RUCONEST	C1 1304	rhC1-INH 100 U/kg	16	No	Yes	NR	NR	1 (5.9)	No	No	No	Yes	0
		Placebo	16			NR	NR	9 (56)					1 (5.9)
	C1 1205	rhC1-INH 100 U/kg	13	No	Yes	NR	NR	0	No	No	No	Yes	0
		rhC1-INH 50 U/kg	12[c]			NR	NR	0					0
		Placebo	13			NR	NR	1 (7.7)					0
	C1 1310	rhC1-INH 50 U/kg	44	Yes	Yes	rhC1-INH 50 U/kg	5 (11.4)	4 (9)	No	Yes	Yes	Yes	8 (18)
		Placebo	31			rhC1-INH 50 U/kg	13 (41.9)	2 (6)					14 (45)
Sebetralstat	KVD900-201	Sequence 1	58	No	Yes	NR	NR	NR	NR	NR	NR	NR	NR
		Sequence 2	55			NR	NR	NR					NR
	KONFIDENT	Sebetralstat 300 mg	87	Yes	Yes	Sebetralstat 300 mg	34 (39.1)	12 (13.8)	Yes	Yes	No	Yes	21 (24.1)
		Sebetralstat 600 mg	93			Sebetralstat 600 mg	37 (39.8)	8 (8.6)					22 (23.7)
		Placebo	84			Placebo	47 (56.0)	21 (25)					43 (51.2)

[a]Rescue was defined as any additional medication given other than the IMP that may have affected observed treatment response. [b]Censored patients are those who received rescue or redosed (if allowed) or other disallowed medication prior to achieving the primary end point. In KONFIDENT, censoring occurred if patients received rescue treatment with conventional therapy or failed to meet the primary end point within 12 hours. [c]The sample size of the ITT population of the rhC1-INH 50 U/kg arm in C1-1205 is 13, but only 12 patients were evaluated.

REDOSING AND RESCUE LEVELS

- **Redosing**: KONFIDENT had the highest redosing rates (39%-40%) in IMP arms, whereas IMPACT-1 had the highest redosing rate in the placebo arm (57.1%). In EDEMA-3, EDEMA-4, and C1 1310, patients receiving IMP or placebo could be redosed with open-label IMP, resulting in censoring, whereas redosing remained blinded in KONFIDENT, thereby preventing censoring of patients (Table 4)
- **Rescue:** EDEMA-4 had the highest rescue therapy use (33.3%) in the IMP arm, whereas C1 1304 had the highest rescue therapy use in the placebo arm (56%)

CENSORING DETAIL AND LEVELS

- **Censoring criteria:** KONFIDENT and EDEMA-3 and EDEMA-4 included censoring as part of the primary end point, right censoring at hours 12 and 4, respectively. KONFIDENT did not censor attacks that needed redosing (Table 4)
- **Censoring**: IMPACT-1 and KONFIDENT trials had higher censoring rates in the IMP arm at 30.2% and 23.7% to 24.1%, respectively. IMPACT-1, KONFIDENT, and C1 1310 had high censoring rates in the placebo arm at 54.8%, 51.2%, and 45%, respectively

TABLE 5 Variability in End Point Definitions Limit Comparability of Trial Results

NR Data are not reported, missing, or could not be found

		END POINT DETAILS					PRO DIMENSIONS			IMPROVEMENT REQUIREMENTS	
IMP	TRIAL	END POINT	PRO	QUESTION STRUCTURE	RESPONSE OPTIONS	SUCCESS CRITERIA	LOCATION	SYMPTOMS	GLOBAL	SUSTAINED	PERSISTENT
Berinert	IMPACT-1	TOSR	NR	Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?	Yes, no	Answer "yes"	No	No	Yes	Yes	NR
Firazyr	FAST-1 and FAST-2		VAS[a]	The subject should draw a vertical line at the point along the scale that represents the current status of the measured symptom	0 mm, no symptom; -100 mm, worst possible symptom	30% reduction in score	Yes	Yes	No	Yes	No
	FAST-3		VAS-3[b]	The subject should draw a vertical line at the point along the scale that represents the current status of the measured symptom	Mean scores for skin swelling, skin pain, and abdominal pain, VAS-3	50% reduction in score	No	Yes	No	Yes	No
RUCONEST	C1 1310		TEQ	Q1: To what extent has the overall severity of your [attack location] HAE attack changed since you received the infusion? Q2: Overall, has the intensity of your [relevant attack location] HAE attack symptoms begun to decrease noticeably since you received the infusion?	Q1: Much worse, Worse, A little worse, No change, A little better, Better, Much Better Q2:Yes, no	Q1: Answer "a little better" or more Q2: Answer "yes" to Q2	Yes	No	No	Yes	Yes
	C1 1205 and C1 1304		VAS	How severe are the angioedema symptoms now for this location?	0 mm meaning ''no symptoms at all'' and 100 mm meaning ''extremely disabling''	≥ 20-mm reduction from baseline	Yes	No	No	Yes	Yes
Sebetralstat	KONFIDENT		PGI-C	How would you describe your overall HAE symptoms right now, compared to how you were when you took the trial medication?	Much worse, worse, a little worse, no change, a little better, better, much better	Rating of at least "a little better" within 12 h	No	No	Yes	Yes	No
	KONFIDENT	TTRS	PGI-S	What is your overall HAE attack severity right now?	None, mild, moderate, severe, very severe	1-point decrease from baseline within 12 h	No	No	Yes	Yes	No
RUCONEST	C1 1310	TTMS	TEQ	Q3: At this moment, are your HAE attack symptoms minimal [barely noticeable]?	Yes, no	Answer "yes"	Yes	No	No	No	No
	C1 1310, C1 1205, and C1 1304		VAS	How severe are the angioedema symptoms now for this location?	0 mm meaning ''no symptoms at all'' and 100 mm meaning ''extremely disabling''	Achieve score < 20 mm	Yes	No	No	No	No
Berinert	IMPACT-1	TTCR	NR	Have all symptoms of the HAE attack resolved completely?	Yes, no	Answer "yes"	No	No	Yes	No	No
Firazyr	FAST-1, FAST-2, and FAST-3		VAS	The subject should draw a vertical line at the point along the scale that represents the current status of the measured symptom	0 mm, no symptom; -100 mm, worst possible symptom	Achieve score <10 mm at all symptoms/locations	No	Yes	No	Yes	No
Sebetralstat	KONFIDENT and KVD900-201		PGI-S	What is your overall HAE attack severity right now?	None, mild, moderate, severe, very severe	Achieve rating of "none" within 24 h	No	No	Yes	No	No
Kalbitor	EDEMA-3/EDEMA-4	NR	MSCS	Describe the severity of the following [symptom complex] at this time?	Normal [0], mild [1], moderate [2], and severe [3] averaged over select locations	Change from baseline MSCS ranging from +2 to -3 at 4 h	Yes	Yes	No	No	No
Kalbitor	EDEMA-3/EDEMA-4	NR	TOS	What [symptom complex(es)] are you experiencing? Describe the severity and level of improvement of [symptom complex] at this time.	Severity = normal [0] to severe [3]; significant improvement/worsening [100 to -100]	Change from baseline TOS at 4 h	Yes	Yes	No	No	No

[a]Most severe symptom was chosen by assessing the most severe "cutaneous swelling" or "pain (skin)"; if these were equal, pain was used. For abdominal attacks, pain was used. [b]Composite of skin pain, skin swelling, and abdominal pain.

END POINT REPORTING

- **Primary end point reporting**: 8 of 12 studies reported TOSR as the primary end point (Table 5)
- **PRO Instruments**: 5 different PRO instruments were used across these 8 studies, each with varying criteria for success (Table 5)

END POINT DEFINITIONS

- **Berinert and sebetralstat trials**: These trials used PRO instruments with global dimensions (Table 5)
- **Kalbitor and Firazyr trials**: These trials used PRO instruments with both location- and symptom-specific dimensions
- **RUCONEST trials**: These trials used PRO instruments that had location-specific dimensions, but not symptom-specific dimensions

CRITERIA FOR SUCCESS

- **RUCONEST Trials**: These trials required both sustained response at multiple time points and persistent improvement (ie, the same or better PRO response) to achieve the primary (TOSR) end point (Table 5)
- **Other Trials**: Both sustained response and persistent improvement were not required in other trials

FUTURE RESEARCH

- **Mapping studies:** Need to connect the dimension of 2 PRO end points to compare clinical trials
- **Trial reanalysis**: Need to reanalyze results using similarly defined end point criteria to compare clinical trials
- **Population adjustment**: Need to adjust for clinically validated effect modifiers across trial populations to compare clinical trials

CONCLUSIONS

- HAE on-demand treatments have been evaluated in 12 trials over the past 15 years
- Variations in methodologies of these 12 trials—including trial design (crossover vs parallel), setting (site vs home), baseline attack characteristics, and use of prophylactic therapies—limit the comparability among studies
- Inconsistencies in protocols for redosing and rescue medication use may have modified observed treatment effects
- Different criteria and high rates of censoring may introduce challenges with interpreting the results of final analyses
- End point definitions across the 12 trials differed considerably and used different PRO instruments with different criteria for success
- Overall, results from these 12 trials remain difficult to compare without further research in mapping studies to connect the dimensions of 2 PRO end points, reanalysis of results using similarly defined end point criteria, and population adjustment for clinically validated effect modifiers across trial populations

ABBREVIATIONS

AAAAI, American Academy of Allergy, Asthma & Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AE, adverse event; C1-INH, C1 esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; IMP, investigational medicinal product; IQR, interquartile range; LTP, long-term prophylaxis; MSCS, mean symptom complex severity; NMA, network meta-analysis; NR, not reported; OLE, open-label extension; OPPL, orofacial, pharyngeal, laryngeal; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PICOS-T, populations, interventions, comparisons, outcomes, study designs, and time; PRO, patient-reported outcome; PT, patient; Q, question; QOL, quality of life; RCT, randomized control trial; rhC1-INH, recombinant human C1 esterase inhibitor; SAE, serious adverse event; SLR, systematic literature review; TEQ, treatment effect questionnaire; TOS, treatment outcome score; TOSR, time to beginning of symptom relief; TTCR, time to complete resolution; TTMS, time to minimal symptoms; TTRS, time to reduced severity; VAS, visual analog scale.

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