Journal: Drugs in R&D

Title: Network Meta-analysis of Pharmacological Therapies for Long-term Prophylactic Treatment of Patients with Hereditary Angioedema

Running Head: NMA of Prophylactic Treatments for Patients with HAE

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Supplementary Information

Appendix A: Systematic Literature Review Methods

Search Strategies

Date of the search: 11 Aug 2022

Database searched:

- Ovid Medline
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily
- Ovid Embase
- Ovid EBM Reviews - Cochrane Central Register of Controlled Trials
- Ovid EBM Reviews - Cochrane Database of Systematic Reviews

Limits:

- Humans
- Opinion pieces removed
- >2 years conference abstracts removed

Filters:
Randomized Studies (both MEDLINE and Embase filters have Phase 2-3 - additional terms to supplement RCTs filter) from:
Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

MEDLINE RCT Filter – Cochrane Handbook, 2019
Box 3.c Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format
https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#section-3-6-1

Embase RCT sensitive Filter – Cochrane Handbook, 2019
Box 3.e Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2018 revision) https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#section-3-6-2

MULTIFILE SEARCH

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2022**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to August 10, 2022**, Embase** 1974 to 2022 August 10**, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to August 10, 2022

Search Strategy:

#	Searches	Results
1	Angioedemas, Hereditary/ or "Hereditary Angioedema Types I and II"/ or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1INHibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1INH-HAE or (heredit$ adj10 (HAE or HANE or C1INH))).ti,ab,kf,kw. [HEREDITARY ANGIOEDEMA]	23735
2	(randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ti,ab. or drug therapy.fs. [RCTs – MEDLINE sensitive Filter – Cochrane HSSS, 2019]	15081198
3	exp Randomized Controlled Trials as Topic/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo$ or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or phase 4 or phase 4a or phase 4b or phase 4c or phase IV or phase IVa or phase IVb or phase IVc or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-4, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2386105
4	2 or 3	15349141
5	1 and 4	12259
6	exp Animals/ not Humans/ [ANIMAL STUDIES ONLY - REMOVE - MEDLINE]	16495684
7	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE]	4705496
8	5 not (6 or 7)	8749
9	8 use ppez [MEDLINE records]	1101
10	(angioneurotic edema/ and heredit$.mp.) or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1INHibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1INH-HAE or (heredit$ adj10 (HAE or HANE or C1INH))).ti,ab,kf,kw. [HEREDITARY ANGIOEDEMA]	9396
11	Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab.	11040298

12	(Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or ((((case adj control$) and random$) not randomi?ed controlled) or (nonrandom$ not random$) or "Random field$" or (random cluster adj3 sampl$)).ti,ab. or (Systematic review not (trial or study)).ti. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))	5694923
13	11 not 12 [RCTS Filter EMBASE - sensitive - Cochrane Handbook]	10068266
14	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo* or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or phase 4 or phase 4a or phase 4b or phase 4c or phase IV or phase IVa or phase IVb or phase IVc or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-4, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2126495
15	10 and (13 or 14)	1733
16	(exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE]	12004450
17	(editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase]	5051801
18	15 not (16 or 17)	1682
19	conference abstract.pt.	4499674
20	18 not 19 [CONFERENCE ABSTRACTS REMOVED]	1115
21	18 and 19	567
22	limit 21 to yr="2020-Current"	87
23	20 or 22 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED]	1202
24	23 use oemezd [Embase records]	481
25	Angioedemas, Hereditary/ or "Hereditary Angioedema Types I and II"/ or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1INHibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1INH-HAE or (heredit$ adj10 (HAE or HANE or C1INH))).ti,ab,kw. [HEREDITARY ANGIOEDEMA]	23693
26	25 use cctr [CENTRAL records]	448
27	((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1INHibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1INH-HAE or (heredit$ adj10 (HAE or HANE or C1INH))).ti,ab,kw. [HEREDITARY ANGIOEDEMA]	8959

28	27 use coch [CDSR records]	3
29	9 or 24 or 26 or 28	2033
30	**remove duplicates from 29**	**1599**

Date of the search: 16 Sept 2024

Update date span:
Aug 2022– Current (MEDLINE, Embase, CDSR databases)
July 2022 – Current (CENTRAL database)

Database searched:

- Ovid Medline
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily
- Ovid Embase
- Ovid EBM Reviews - Cochrane Central Register of Controlled Trials
- Ovid EBM Reviews - Cochrane Database of Systematic Reviews

Limits:

Humans
Opinion pieces removed
Conference abstracts retained for 2023 – Current; in Embase & CENTRAL
Date limit: July/Aug 2022 – Current

Filters:
Randomized Studies (both MEDLINE and Embase filters have Phase 2-3 - additional terms to supplement RCTs filter) from:
Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

MEDLINE RCT Filter – Cochrane Handbook, 2019
Box 3.c Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format
https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#section-3-6-1

Embase RCT sensitive Filter – Cochrane Handbook, 2019
Box 3.e Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2018 revision) https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#section-3-6-2

MULTIFILE SEARCH

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2024**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to September 5, 2024**, Embase** 1974 to 2024 September 13**, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions** 1946 to September 13, 2024

Search Strategy:

#	Searches	Results
1	Angioedemas, Hereditary/ or "Hereditary Angioedema Types I and II"/ or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1-inhibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1-INH-HAE or (heredit$ adj10 (HAE or HANE or C1-INH))).ti,ab,kf,kw. [HEREDITARY ANGIOEDEMA]	26973
2	(randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ti,ab. or drug therapy.fs. [RCTs – MEDLINE sensitive Filter – Cochrane HSSS, 2019]	16914660
3	exp Randomized Controlled Trials as Topic/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo$ or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or phase 4 or phase 4a or phase 4b or phase 4c or phase IV or phase IVa or phase IVb or phase IVc or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-4, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2749948
4	2 or 3	17236429
5	1 and 4	13832
6	exp Animals/ not Humans/ [ANIMAL STUDIES ONLY - REMOVE - MEDLINE]	17087759
7	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE]	5131498
8	5 not (6 or 7)	10144
9	8 use ppezv [MEDLINE records]	1244
10	(angioneurotic edema/ and heredit$.mp.) or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1-inhibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1-INH-HAE or (heredit$ adj10 (HAE or HANE or C1-INH))).ti,ab,kf,kw. [HEREDITARY ANGIOEDEMA]	10633
11	Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab.	12649775

12	(Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or ((((case adj control$) and random$) not randomi?ed controlled) or (nonrandom$ not random$) or "Random field$" or (random cluster adj3 sampl$)).ti,ab. or (Systematic review not (trial or study)).ti. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))	6673177
13	11 not 12 [RCTS Filter EMBASE - sensitive - Cochrane Handbook]	11474742
14	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo* or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or phase 4 or phase 4a or phase 4b or phase 4c or phase IV or phase IVa or phase IVb or phase IVc or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-4, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2431768
15	10 and (13 or 14)	2008
16	(exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE]	12799569
17	(editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase]	5549937
18	15 not (16 or 17)	1951
19	conference abstract.pt.	5230026
20	18 not 19 [CONFERENCE ABSTRACTS REMOVED]	1305
21	18 and 19	646
22	limit 21 to yr="2023-Current"	61
23	20 or 22 [LAST >2 YRS OF CONFERENCE ABSTRACTS RETAINED]	1366
24	23 use oemezd [Embase records]	520
25	Angioedemas, Hereditary/ or "Hereditary Angioedema Types I and II"/ or ((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1-inhibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1-INH-HAE or (heredit$ adj10 (HAE or HANE or C1-INH))).ti,ab,kw. [HEREDITARY ANGIOEDEMA]	26921
26	(editorial or note or comment).pt. or (letter.pt. not randomized controlled trial/) [OPINION PIECES REMOVE - CENTRAL]	5455492
27	25 not 26 [OPINION PIECES REMOVED - CENTRAL]	24206
28	Conference proceeding.pt. [CONFERENCE ABSTRACTS/PROCEEDINGS]	244835
29	27 and 28 [CONFERENCE ABSTRACTS ONLY]	197
30	limit 29 to yr="2023-Current"	21
31	27 not 28 [CONFERENCE ABSTRACTS REMOVED]	24009
32	30 or 31 [LAST >2 YRS OF CONFERENCE ABSTRACTS RETAINED]	24030

33	32 use cctr [CENTRAL records]	319
34	((heredit$ adj4 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or (heredit$ adj4 acute adj2 (circumscribe$ or essential) adj2 (edema? or oedema?)) or (heredit$ adj4 angioneurotic$ adj3 (swell$ or syndrome?)) or (heredit$ adj4 (quincke or neurogenic$ or wandering) adj2 (edema? or oedema?)) or (heredit$ adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica$)) or (("C1-inhibitor" or "C1-esterase-inhibitor") adj8 (angioedema$ or angio-oedema$ or angioedema$ or angiooedema$ or angioneurotic$ or angio-neurotic$)) or C1-INH-HAE or (heredit$ adj10 (HAE or HANE or C1-INH))).ti,ab,kw. [HEREDITARY ANGIOEDEMA]	10139
35	34 use coch [CDSR records]	3
36	9 or 24 or 33 or 35	2086
37	limit 9 to dt="20220801-20241231" [MEDLINE update results: Aug 2022-Current]	143
38	limit 24 to dc="20220801-20241231" [Embase update results: Aug 2022-Current]	134
39	33 and (202207$ or 202208$ or 202209$ or 202210$ or 202211$ or 202212$ or 2023$ or 2024$).up. [CENTRAL update results: July 2022-Current]	137
40	35 and (202208$ or 202209$ or 202210$ or 202211$ or 202212$ or 2023$ or 2024$).up. [CDSR update results: Aug 2022-Current]	2
41	or/37-40	416
42	limit 41 to yr="2022 -Current"	331
43	**remove duplicates from 42**	**250**

PICOS

Supplementary Table 1: PICOS criteria

	Inclusion Criteria	Exclusion Criteria
Population	Study populations or subgroups of patients (humans only; men or women) with: • Age ≥ 12 years • Diagnosed with HAE, type I or II	Study populations or subgroups: • Non-human • Age <12 years • No confirmation of HAE

Interventions	The following treatments available/widely approved or under investigation for HAE as prophylaxis, provided as a single-agent:
	• garadacimab
	• C1 esterase inhibitor human preparations:
	  ○ IV (Cinryze)
	  ○ SC (Berinert, or Haegarda in North America)
	• lanadelumab (Takhzyro)
	• berotralstat (Orladeyo)
		• Combination of treatments listed in the *Inclusion Criteria*
		• Those not listed in the *Inclusion Criteria*

Comparators	The comparator may be one of the treatments outlined above (i.e., in a head-to-head) or placebo	• Combination of treatments listed in the *Inclusion Criteria* • Those not listed in the *Inclusion Criteria*
Outcomes	The following outcomes will be investigated: • Time-normalized no. of HAE attacks • N and % attack-free patients • Time-normalized no. of attacks requiring on-demand treatment • Time-normalized no. of moderate and/or severe HAE attacks • N and % of subjects with adverse events • N and % of subjects with serious adverse events • N and % mortality • N and % discontinuations due to AEs • N and % discontinuations from the trial • AE-QoL	• Those not listed in the *Inclusion Criteria*
Study Design	Studies with the following designs: • RCTs irrespective of blinding status	Studies with the following designs: • Non-randomized clinical trials • Phase I trials • Observational studies (e.g., RWE, registry, retrospective cohort, cross-sectional, case-control/series/reports, single-arm) • Pre-clinical studies, reports, expert opinion articles, letters, narrative (non-systematic) reviews, editorials, pilot studies, protocols • Pharmacokinetic studies • SLRs[a]
Language	Articles in English	All non-English articles[b]

	Inclusion Criteria	Exclusion Criteria
Dates	• Databases: Inception-present • Conference abstracts: 2020-present	• Databases: None • Conference abstracts: Prior to 2020

[a] Relevant SLRs will not be included in the final included studies list; however, bibliographies of the two most recent and relevant SLRs will be reviewed for any additional studies; data from these SLRs will not be extracted.
[b] Search strategy will not be limited by language.
Abbreviations: AEs = adverse events; AE-QoL = The Angioedema Quality of Life questionnaire; HAE = hereditary angioedema; IV = intravenous; N = number; PICOS = Population, Intervention, Comparator, Outcome, Study design; RCT = randomized controlled trial; RWE = real-world evidence; SC = subcutaneous; SLR = systematic literature review.

Sources Searched

Supplementary Table 2: Selected Databases and Grey Literature Sources

Search Engine	Database
Ovid	• Embase • MEDLINE® • MEDLINE® In-Process, Epub Ahead of Print, In-Process and other Non-Indexed Citations, and Daily • Cochrane Central Register of Controlled Trials • Cochrane Database of Systematic Reviews
Other Sources	• ClincialTrials.gov • Bibliographic search[a]

[a] Bibliographies of the two most recent and relevant SLRs were reviewed for any additional studies; data from these SLRs were not extracted.
Abbreviations: MEDLINE = Medical Literature Analysis and Retrieval System Online

Included Studies

Supplementary Table 3: Included Studies

Trial Name	Trial ID	Citation	Source
VANGUARD[a]	NCT04656418	CSL Behring, "253590_CSL312_3001_Final_Tables_20220829," 2022. Accessed: October 7, 2022.	Other sources
		"CSL312 (Garadacimab) in the Prevention of Hereditary Angioedema Attacks (NCT04656418)." Clinicaltrials.gov https://ClinicalTrials.gov/show/NCT04656418	ClinicalTrials.gov
		T.J. Craig *et al.,* "Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial," The Lancet, vol. 401, no. 10382, pp. 1079–1090, 2023, doi: https://dx.doi.org/10.1016/S0140-6736%2823%2900739-0.	Database search
		T. Craig *et al.*, "Efficacy and Safety of Subcutaneous Garadacimab for the Prophylaxis of Hereditary Angioedema Attacks in Adults and Adolescent Patients with HAE: Results from a Multicenter, Placebo-Controlled Phase 3 Trial," Journal of Allergy and Clinical Immunology, vol. 151, no. 2 Supplement, p. AB132, 2023, doi: https://dx.doi.org/10.1016/j.jaci.2022.12.414.	Database search
		"Erratum: Department of Error (The Lancet (2023) 401(10382) (1079–1090), (S0140673623003501), (10.1016/S0140-6736(23)00350-1))," The Lancet, vol. 401, no. 10384, p. 1266, 2023, doi: https://dx.doi.org/10.1016/S0140-6736%2823%2900739-0.	Database search
NA[a]	NCT03712228	T. Craig *et al.*, "Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial," (in English), *The Lancet,* vol. 399, no. 10328, pp. 945-955, 2022, doi: https://dx.doi.org/10.1016/S0140-6736%2821%2902225-X.	Database search
		"A Study to Investigate CSL312 in Subjects With Hereditary Angioedema (HAE) (NCT03712228)." Clinicaltrials.gov. https://ClinicalTrials.gov/show/NCT03712228	ClinicalTrials.gov
		T.J. Craig *et al.,* "Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study," The Lancet Haematology, vol. 11, no. 6, pp. e436–e447, 2024, doi: https://dx.doi.org/10.1016/S2352-3026%2824%2900081-4.	Database search

Trial Name	Trial ID	Citation	Source
		M. Magerl *et al*., “Efficacy and safety of garadacimab in patients with hereditary angioedema in a phase 2 open-label extension study,” Allergy: European Journal of Allergy and Clinical Immunology, vol. 78, Supplement 111, p. 603, 2023, doi: https://dx.doi.org/10.1111/all.15616.	Database search
		T. Craig, M. Magerl, D.S. Levy, A. Reshef, W.R. Lumry, I. Martinez-Saguer, J.S. Jacobs, W.H. Yang, B. Ritchie, E. Aygoren-Pursun, P.K. Keith, P. Busse, H. Feuersenger, D. Pawaskar, I. Jacobs, I. Pragst, M.K. Doyle, “Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial,” Lancet (London, England), vol. 399, no. 10328, p. 945, 2022, doi: https://doi.org/10.1016/S0140-6736(21)02225-X.	Database search
APeX-1	NCT02870972	E. Aygoren-Pursun *et al.*, "Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema," (in English), *New England Journal of Medicine,* vol. 379, no. 4, pp. 352-362, 2018, doi: https://dx.doi.org/10.1056/NEJMoa1716995.	Database search
		"Efficacy and Safety of BCX7353 to Prevent Angioedema Attacks in Subjects With Hereditary Angioedema (APeX-1) (NCT02870972)." Clinialtrials.gov. https://clinicaltrials.gov/ct2/show/NCT02870972	ClinicalTrials.gov
APeX-2	NCT03485911	H. J. Wedner *et al.*, "Sustained Reductions in Hereditary Angioedema (HAE) Attack Rates Observed over 96 Weeks of Oral Berotralstat Treatment Regardless of Initial Response," (in English), *Journal of Allergy and Clinical Immunology,* vol. 149, no. 2 Supplement, p. AB164, 2022, doi: https://dx.doi.org/10.1016/j.jaci.2021.12.543.	Database search
		E. Aygoren-Pursun, D. McNeil, P. Collis, B. Desai, D. Tomita, and D. Johnston, "Oral Berotralstat Treatment for 96 Weeks Consistently Reduces Hereditary Angioedema (HAE) Attack Rates Regardless of Baseline Attack Rate," (in English), *Journal of Allergy and Clinical Immunology,* vol. 149, no. 2 Supplement, p. AB164, 2022, doi: https://dx.doi.org/10.1016/j.jaci.2021.12.544.	Database search
		B. Zuraw *et al.*, "Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial," (in English), *Journal of Allergy and Clinical Immunology,* vol. 148, no. 1, pp. 164-172.e9, 2021, doi: https://dx.doi.org/10.1016/j.jaci.2020.10.015.	Database search
		H. J. Wedner *et al.*, "Randomized Trial of the Efficacy and Safety of Berotralstat (BCX7353) as an Oral Prophylactic Therapy for Hereditary Angioedema: Results of APeX-2 Through 48 Weeks (Part 2)," (in English),	Database search

Trial Name	Trial ID	Citation	Source
		Journal of Allergy and Clinical Immunology: In Practice, vol. 9, no. 6, pp. 2305-2314.e4, 2021, doi: https://dx.doi.org/10.1016/j.jaip.2021.03.057.	
		H. H. Li, J. Best, S. Murray, H. Iocca, and R. Tachdijan, "Berotralstat Consistently Demonstrates Reductions in Attack Frequency in Hereditary Angioedema (HAE) Irrespective of Baseline Attack Rate: Subgroup Analysis from the APeX-2 Trial," (in English), *Journal of Allergy and Clinical Immunology,* vol. 147, no. 2 Supplement, p. AB22, 2021, doi: https://dx.doi.org/10.1016/j.jaci.2020.12.118.	Database search
		S. Kiani *et al.*, "Durable reduction in hereditary angioedema (HAE) attack rates with berotralstat over 24 months: Results from the phase 3 apeX-2 study," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 76, no. SUPPL 110, p. 16, 2021, doi: https://dx.doi.org/10.1111/all.15093.	Database search
		J. Anderson, R. Gagnon, J. Best, S. Murray, H. Iocca, and K. Sitz, "Reduction in Attacks in Hereditary Angioedema (HAE) With Berotralstat is Consistent Regardless of Prior Prophylactic Treatment: A Subgroup Analysis of the Phase 3 APeX-2 Trial," (in English), *Journal of Allergy and Clinical Immunology,* vol. 147, no. 2 Supplement, p. AB23, 2021, doi: https://dx.doi.org/10.1016/j.jaci.2020.12.122.	Database search
		H. Wedner *et al.*, "BEROTRALSTAT REDUCES ATTACKS IN PATIENTS WITH HEREDITARY ANGIOEDEMA (HAE): APEX-2 TRIAL 48 WEEK RESULTS," (in English), *Annals of Allergy, Asthma and Immunology,* vol. 125, no. 5 Supplement, p. S14, 2020, doi: https://dx.doi.org/10.1016/j.anai.2020.08.063.	Database search
		W. Lumry *et al.*, "Relative Reductions in Attack Rate With Prophylactic Berotralstat (BCX7353) in Subjects with Hereditary Angioedema (HAE): Responder Analysis from the APeX-2 Study," (in English), *Journal of Allergy and Clinical Immunology,* vol. 145, no. 2 Supplement, p. AB105, 2020, doi: https://dx.doi.org/10.1016/j.jaci.2019.12.630.	Database search
		D. Johnston *et al.*, "Gastrointestinal (GI) Adverse Events (AEs) Observed With Berotralstat (BCX7353) Treatment for Hereditary Angioedema (HAE) are Primarily Mild, Self-limited, and Diminish with Time on Treatment," (in English), *Journal of Allergy and Clinical Immunology,* vol. 145, no. 2 Supplement, p. AB102, 2020, doi: https://dx.doi.org/10.1016/j.jaci.2019.12.619.	Database search
		D. Johnston *et al.*, "BEROTRALSTAT IMPROVES PATIENT-REPORTED QUALITY OF LIFE THROUGH 48 WEEKS IN THE PHASE 3 APEX-2 TRIAL," (in English), *Annals of Allergy, Asthma and Immunology,* vol. 125,	Database search

Trial Name	Trial ID	Citation	Source
		no. 5 Supplement, p. S22, 2020, doi: https://dx.doi.org/10.1016/j.anai.2020.08.087.	
		J. Bernstein *et al.*, "Oral Prophylaxis with Berotralstat (BCX7353) Reduces Use of Standard of Care (SOC) On-demand Medication in Patients with Hereditary Angioedema (HAE): APeX-2 Study Results," (in English), *Journal of Allergy and Clinical Immunology,* vol. 145, no. 2 Supplement, p. AB106, 2020, doi: https://dx.doi.org/10.1016/j.jaci.2019.12.632.	Database search
		E. Aygoren-Pursun *et al.*, "Berotralstat (BCX7353) treatment demonstrates robust and durable reduction in the rate of hereditary angioedema (HAE) attacks over 48 weeks of the phase 3 APeX-2 study," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 75, no. SUPPL 109, pp. 457-458, 2020, doi: https://dx.doi.org/10.1111/all.14508.	Database search
		"Efficacy and Safety Study of BCX7353 as an Oral Treatment for the Prevention of Attacks in HAE (APeX-2) (NCT03485911)." https://ClinicalTrials.gov/show/NCT03485911	ClinicalTrials.gov
APeX-J	NCT03873116	I. Ohsawa *et al.*, "Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 76, no. 6, pp. 1789-1799, 2021, doi: https://dx.doi.org/10.1111/all.14670.	Database search
		"Study to Evaluate the Efficacy and Safety of BCX7353 as an Oral Treatment for the Prevention of HAE Attacks in Japan." https://ClinicalTrials.gov/show/NCT03873116	ClinicalTrials.gov
		D. Honda *et al.,* "Berotralstat for long-term prophylaxis of hereditary angioedema in Japan: Parts 2 and 3 of the randomized APeX-J Phase III trial," World Allergy Organization Journal, vol. 17, no. 3, p. 100882, 2024, doi: https://dx.doi.org/10.1111/all.15616.	Database search
COMPACT[b]	NCT01912456	H. H. Li *et al.*, "Subcutaneous C1 inhibitor for prevention of attacks of hereditary angioedema: Additional outcomes and subgroup analysis of a placebo-controlled randomized study," (in English), *Allergy, Asthma and Clinical Immunology,* vol. 15, no. 1, p. 49, 2019, doi: https://dx.doi.org/10.1186/s13223-019-0362-1.	Database search
		H. H. Li *et al.*, "Subcutaneous C1-esterase inhibitor to prevent hereditary angioedema attacks: Safety findings from the COMPACT trial," (in English), *Allergy and Asthma Proceedings,* vol. 39, no. 5, pp. 365-370, 2018, doi: https://dx.doi.org/10.2500/aap.2018.39.4164.	Database search
		H. Longhurst *et al.*, "Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor," (in English), *New England Journal of*	Database search

Trial Name	Trial ID	Citation	Source
		Medicine, vol. 376, no. 12, pp. 1131-1140, 2017, doi: https://dx.doi.org/10.1056/NEJMoa1613627.	
		"A Study to Evaluate the Clinical Efficacy and Safety of Subcutaneously Administered C1-esterase Inhibitor in the Prevention of Hereditary Angioedema (NCT01912456)." Clinicaltrials.gov. https://ClinicalTrials.gov/show/NCT01912456	ClinicalTrials.gov
COMPACT OLE	NCT02316353	D. Levy *et al.*, "Long-Term Efficacy of Subcutaneous C1 Inhibitor in Pediatric Patients with Hereditary Angioedema," (in English), *Pediatric, Allergy, Immunology, and Pulmonology,* vol. 33, no. 3, pp. 136-141, 2020, doi: https://dx.doi.org/10.1089/ped.2020.1143.	Database search
		J. A. Bernstein *et al.*, "Long-term safety and efficacy of subcutaneous C1INHibitor in older patients with hereditary angioedema," (in English), *Annals of Allergy, Asthma and Immunology,* vol. 125, no. 3, pp. 334-340.e1, 2020, doi: https://dx.doi.org/10.1016/j.anai.2020.05.015.	Database search
HELP	NCT02586805	W. Lumry *et al.*, "Lanadelumab efficacy and safety after switching from androgens: analysis of the phase 3 HELP and HELP OLE studies for hereditary angioedema," (in English), *Journal of Allergy and Clinical Immunology,* vol. 149, no. 2 Supplement, p. AB166, 2022, doi: https://dx.doi.org/10.1016/j.jaci.2021.12.551.	Database search
		W. R. Lumry *et al.*, "Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 76, no. 4, pp. 1188-1198, 2021, doi: https://dx.doi.org/10.1111/all.14680.	Database search
		M. Riedl *et al.*, "Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 75, no. 11, pp. 2879-2887, 2020, doi: https://dx.doi.org/10.1111/all.14416.	Database search
		S. Kiani-Alikhan *et al.*, "Efficacy of lanadelumab is durable over time: Findings from the HELP Study and HELP OLE," (in English), *Allergy: European Journal of Allergy and Clinical Immunology,* vol. 75, no. SUPPL 109, p. 59, 2020, doi: https://dx.doi.org/10.1111/all.14504.	Database search
		P. Busse, R. Tachdjian, H. Longhurst, P. Lu, C. Nurse, and J. Anderson, "Long-term Efficacy and Safety of Lanadelumab for Prophylactic Treatment in Adolescent Patients with Hereditary Angioedema (HAE)," (in English), *Journal of Allergy and Clinical Immunology,* vol. 145, no. 2 Supplement, p. AB103, 2020, doi: https://dx.doi.org/10.1016/j.jaci.2019.12.623.	Database search

Trial Name	Trial ID	Citation	Source
		A. Banerji *et al.*, "Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial," (in English), *JAMA - Journal of the American Medical Association,* vol. 320, no. 20, pp. 2108-2121, 2018, doi: https://dx.doi.org/10.1001/jama.2018.16773.	Database search
		"Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE (NCT02586805)." Clinicaltrials.gov. https://ClinicalTrials.gov/show/NCT02586805	ClinicalTrials.gov
		T.J. Craig, R.H. Zaragoza-Urdaz, H.H. Li, M. Yu, H. Ren, S. Juethner, J. Anderson, "Effectiveness and safety of lanadelumab in ethnic and racial minority subgroups of patients with hereditary angioedema: results from phase 3 studies," Allergy, Asthma and Clinical Immunology, vol. 18, no. 1, p. 85, 2022, doi: https://dx.doi.org/10.1186/s13223-022-00721-y.	Database search

[a] Additional unpublished data from the VANGUARD and Phase 2 trials for garadacimab was provided by **CSL Behring** (*data on file*).

[b] Additional unpublished data for the pre-crossover population from the included study for subcutaneous C1INH (Berinert, or Haegarda in North America) was provided by ***CSL Behring*** *(data on file)*.

Abbreviations: NA = not available.

Excluded Studies

Supplementary Table 4: Excluded Studies with Reasons

Citation	What is the reason for exclusion?
Date of the search: 11 Aug 2022	
Maurer M, Zanichelli A, Hao J, Inhaber N, Yu M, Hebert J, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. Allergy: European Journal of Allergy and Clinical Immunology. 2022;77(3):979-90.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Gower R, Banerji A, Collis P, Desai B, Tomita D, Lumry W. Sustained Improvement Observed in Patient-Reported Quality of Life (QoL) with 96 Weeks of Oral Berotralstat Treatment. Journal of Allergy and Clinical Immunology. 2022;149(2 Supplement):AB164.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Feuersenger H, Pragst I, Dang J. Prophylactic therapy with subcutaneous C1-inhibitor is associated with sustained symptom control in patients with hereditary angioedema. Allergy and Asthma Proceedings. 2022;43(3):202-8.	Population
Watt M, Maurer M, Devercelli G, Paes K, Regnault A, Meunier J, et al. Long-term Impact of Lanadelumab on Patients with Hereditary Angioedema (HAE) Type 1/2: Patient Reported Outcome (PRO) Findings from the HELP Open-label Extension Study (OLE). Journal of Allergy and Clinical Immunology. 2021;147(2 Supplement):AB24.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Rosi-Schumacher M, Shah SJ, Craig T, Goyal N. Clinical manifestations of hereditary angioedema and a systematic review of treatment options. Laryngoscope investigative otolaryngology. 2021;6(3):394-403.	On topic SLR/MA/NMA
Paes K, Bernstein J, Longhurst H, Aygoren-Pursun E, Ren H, Craig T. Efficacy of Lanadelumab in Hereditary Angioedema Patients With and Without Prior Use of Long-Term Prophylaxis: Final Results From the HELP Open-Label Extension Study. Journal of Allergy and Clinical Immunology. 2021;147(2 Supplement):AB145.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Maurer M, Cancian M, Kiani S, Kinaciyan T, Peter J, Reshef A, et al. Berotralstat reduces hereditary angioedema attack rates regardless of previous prophylaxis. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):214.	Study design (non-RCT, opinion, commentary,

Citation	What is the reason for exclusion?
	single-arm, etc)
Maurer M, Bernstein JA, Jacobs J, Lumry WR, Ren H, Soteres D, et al. Long-term prevention of attacks with lanadelumab across subgroups of patients with hereditary angioedema (HAE): Final results from the HELP open-label extension study. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):10.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Magerl M, Johnston DT, Lumry WR, Bernstein JA, Nurse C, Yu M, et al. Attack-free status during steady state of lanadelumab treatment in patients with hereditary angioedema: Findings from the HELP open-label extension study. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):620.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet Journal of Rare Diseases. 2021;16(1):86.	Population
Levy DS, Bouillet L, Desai B, Aggarwal K, Murray SC, Tachdjian R. Reduction in on-demand medications in patients with hereditary angioedema (HAE) treated with berotralstat. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):622.	Outcome
Kinaciyan T, Sheridan W, Desai B, Tomita D, Grivcheva-Panovska V. SUSTAINED REDUCTION IN HEREDITARY ANGIOEDEMA ATTACK RATES FOLLOWING SWITCH TO BEROTRALSTAT: SUBGROUP ANALYSIS FROM APEX-2. Annals of Allergy, Asthma and Immunology. 2021;127(5 Supplement):S29.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Kiani S, Wu A, Peter J, Reshef A, Maurer M, Stobiecki M, et al. Long-term safety and effectiveness of berotralstat (BCX7353) for the prophylaxis of hereditary angioedema (HAE) attacks: Results from the APeX-S study. Clinical and Experimental Allergy. 2021;51(1):172-3.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Gower R, Busse P, Best J, Murray S, Iocca H, Kinaciyan T. Berotralstat Reduces Use of On-demand Medication in Hereditary Angioedema (HAE) Patients Previously	Outcome

Citation	What is the reason for exclusion?
Treated with Prophylactic Therapies. Journal of Allergy and Clinical Immunology. 2021;147(2 Supplement):AB146.	
Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygoren-Pursun E, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. Clinical and Translational Allergy. 2021;11(4):e12035.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Desai B, Bernstein J, Johnston DT, Aggarwal K, Tomita D, Reshef A. Berotralstat demonstrates consistently low attack rates in adolescent patients: Subgroup analysis from apeX-S. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):621.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Bouillet L, Bocquet A, Belbezier A, Boccon-Gibod I. Effectiveness of lanadelumab in patients with hereditary angioedema with normal C1 inhibitor and FXII mutation. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2021;127(3):391-2.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Alves PB. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. Revista portuguesa de imunoalergologia. 2021;29(3):219.	Non-English
CSL312 (garadacimab) in the prevention of hereditary angioedema attacks. A multicenter, double-blind, randomized, placebo-controlled, parallel-arm study to investigate the efficacy and safety of subcutaneous administration of CSL312 (garadacimab) in the prophylactic treatment of hereditary angioedema. 2021.	Other; Protocol
Riedl M, Johnston D, Lumry W, Bernstein J, Nurse C, Lu P, et al. Attack-Free Status of Patients With Hereditary Angioedema (HAE) During Extended Treatment With Lanadelumab in the HELP OLE Study. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB104.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Reshef A, Maurer M, Kiani S, Wu AY, Stobiecki M, Kinaciyan T, et al. Long-term effectiveness of berotralstat (BCX7353) for the prophylaxis of hereditary angioedema (HAE) attacks: Results from the APeX-S study. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):91-2.	Study design (non-RCT, opinion, commentary,

Citation	What is the reason for exclusion?
	single-arm, etc)
Paes K, Craig T, Bernstein J, Longhurst H, Aygoren-Pursun E, Nurse C, et al. Efficacy of Lanadelumab in Hereditary Angioedema Patients With and Without Prior Long-Term Prophylaxis Use: Interim Results From the HELP Open-Label Extension Study. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB102.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Maurer M, Lumry WR, Li HH, Jacobs J, Soteres D, Lu P, et al. Lanadelumab is well-tolerated and effective across patient subgroups: Findings from the HELP open-label extension study. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):60.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Li H, Feuersenger H, Chiao J. Factors Associated With Reduced Response to Subcutaneous C1-Inhibitor in Patients With Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB108.	Population
Levy DS, Farkas H, Riedl MA, Hsu FI, Brooks JP, Cicardi M, et al. Long-term efficacy and safety of subcutaneous C1-inhibitor in women with hereditary angioedema: Subgroup analysis from an open-label extension of a phase 3 trial. Allergy, Asthma and Clinical Immunology. 2020;16(1):8.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Jacobs J, Aygoren-Pursun E, Sitz K, Tachdjian R, Li H, Best J, et al. BEROTRALSTAT POSITIVELY IMPACTS PATIENT-REPORTED SATISFACTION: RESULTS FROM THE PHASE 3 APEX-2 TRIAL. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S25.	Outcome
Farkas H, Wu AY, Kiani S, Reshef A, Stobiecki M, Kinaciyan T, et al. Long-term safety and tolerability of Berotralstat (BCX7353) for Hereditary Angioedema (HAE) prophylaxis: APeX-S study results. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):58-9.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Soteres D, Anderson J, Paes K, Hao J, Hashemi L, et al. QUALITY OF LIFE OF HEREDITARY ANGIOEDEMA (HAE) PATIENTS WITH DEPRESSION OR ANXIETY RECEIVING LANADELUMAB. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S25.	Study design (non-RCT, opinion, commentary,

Citation	What is the reason for exclusion?
	single-arm, etc)
Craig T, Feuersenger H, Pragst I. Durability of symptom control with long-term prophylactic therapy with subcutaneous c1-inhibitor in patients with hereditary angioedema. Allergy and Asthma Proceedings. 2020;41(6):458-9.	Population
Chiao J, Craig T, Feuersenger H. Weight-based Dosing of Subcutaneous C1-Inhibitor Facilitates Management of Hereditary Angioedema in Obese Patients. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB106.	Population
Burnham K, Reinert JP. Thromboembolic Risk of C1 Esterase Inhibitors: A Systematic Review on Current Evidence. Expert Review of Clinical Pharmacology. 2020;13(7):779-86.	On topic SLR/MA/NMA
Banerji A, Hao J, Yu M, Bernstein J, Johnston D, Riedl M. LONG-TERM EFFICACY AND SAFETY OF LANADELUMAB: FINAL RESULTS FROM THE HELP OPEN-LABEL EXTENSION STUDY. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S21.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Aygoren-Pursun E, Johnston D, Lumry W, Li H, Banerji A, Zuraw B, et al. Patterns of Treatment and Retreatment of Acute Attacks of Hereditary Angioedema (HAE) with Standard of Care (SOC) On-Demand Medication: Results from the APeX-2 Study. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB107.	Outcome
CSL312 (garadacimab) in the prevention of hereditary angioedema attacks. A multicenter, double-blind, randomized, placebo-controlled, parallel-arm study to investigate the efficacy and safety of subcutaneous administration of CSL312 (garadacimab) in the prophylactic treatment of hereditary angioedema. 2020.	Other; Protocol
Zuraw B, Craig T, Cicardi M, Longhurst H, Feuersenger H, Prusty S, et al. Long-term efficacy of subcutaneous c1-inhibitor in patients with hereditary angioedema and very high attack burden. Internal medicine journal. 2019;49:27.	Other; Outdated abstract
Yang WH, Bernstein JA, Riedl MA, Johnston DT, Tang Y, Schranz J, et al. Fixed-Dose Subcutaneous C1-Inhibitor Liquid for Prophylactic Treatment of C1-INH-HAE: SAHARA Randomized Study. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(5):1610-8.e4.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Wang Y, Marier JF, Kassir N, Gosselin NH, Martin P. Exposure-Response Analyses of Lanadelumab in Patients with Hereditary Angioedema. Exposure-Response Analyses of Lanadelumab in Patients with Hereditary Angioedema. 2019;143(2):AB40.	Other; Outdated abstract

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Stobiecki M, Aygoren-Pursun E, Andarawewa S, Zanichelli A, Cicardi M, Huissoon A, et al. Clinical evaluation of pharmacokinetics, pharmacodynamics, safety, and efcacy dose-response of BCX7353 as an acute treatment for angioedema in patients with hereditary angioedema (HAE). Allergy, asthma and clinical immunology. 2019;15.	Other; Outdated abstract
Sexton DJ, Brown NJ, Lumry WR, Gower RG, Hao J, Lu P, et al. Lanadelumab And Cardiovascular Risk: findings From The Phase 3 HELP Study. Lanadelumab And Cardiovascular Risk: findings From The Phase 3 HELP Study. 2019;143(2):AB45.	Outcome
Riedl M, Lumry W, Banerji A, Aygoren-Pursun E, Bernstein J, Maurer M, et al. SAFETY AND TOLERABILITY OF ONCE-DAILY ORAL KALLIKREIN INHIBITOR BCX7353 IN PHASE 3 APEX-2 HAE STUDY. Annals of allergy, asthma and immunology. 2019;123(5):S28.	Other; Outdated abstract
Maurer M, Riedl MA, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema (HAE) attacks in the phase 3 HELP study: findings for days 0-69 and at steady state. Allergy. 2019;74:209.	Other; Outdated abstract
Lumry W, Maurer M, Magerl M, Jain G, Devercelli G, Regnault A, et al. LONG-TERM LANADELUMAB TREATMENT IMPROVES HEALTH-RELATED QUALITY OF LIFE: HELP OPEN-LABEL EXTENSION STUDY INTERIM FINDINGS. LONG-TERM LANADELUMAB TREATMENT IMPROVES HEALTH-RELATED QUALITY OF LIFE: HELP OPEN-LABEL EXTENSION STUDY INTERIM FINDINGS. 2019;123(5):S29.	Other; Outdated abstract
Longhurst HJ, Stobiecki M, Zanichelli A, Huissoon A, Moldovan D, Maurer M, et al. Final results from the ZENITH-1 study: oral administration of plasma kallikrein inhibitor BCX7353 for the treatment of attacks in patients with hereditary angioedema. Allergy. 2019;74:10.	Other; Outdated abstract
Longhurst H, Moldovan D, Bygum A, Cicardi M, Huissoon A, Aygoren-Pursun E, et al. Oral Plasma Kallikrein Inhibitor BCX7353 is Safe and Effective as an On-Demand Treatment of Angioedema Attacks in Hereditary Angioedema (HAE) Patients: results of the ZENITH-1 Trial. Journal of allergy and clinical immunology. 2019;143(2):AB36.	Other; Outdated abstract
Li HH, Craig T, Chiao J, Pragst I, Bonagua E. Long-term safety of subcutaneous C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema. Allergy and asthma proceedings. 2019;40(5):358.	Other; Outdated abstract
Levy DS, Craig T, Longhurst H, Cicardi M, Chiao J, Feuersenger H, et al. Effects of long-term prophylaxis with subcutaneous C1 inhibitor in special patient populations: findings from the COMPACT openlabel extension trial. Allergy. 2019;74:10.	Other; Outdated abstract
Levy D, Chiao J, Dang J, Hood C, Feuersenger H. Patterns of on-demand medication use among patients with hereditary angioedema treated long-term with prophylactic	Other; Outdated abstract

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subcutaneous c1-inhibitor. Journal of managed care and specialty pharmacy. 2019;25:S97.	
Katelaris C, Prusty S. Efficacy and safety of subcutaneous C1-inhibitor in Australian patients with hereditary angioedema. Internal medicine journal. 2019;49:27.	Other; Outdated abstract
Kapoor A, Zhou Z, Sexton D, Paes K, Lu P, Chockalingam P. Functional C1-Esterase inhibitor and complement protein 4 levels were not altered by lanadelumab treatment in HAE patients in the phase 3 HELP study. Allergy, asthma and clinical immunology. 2019;15.	Other; Outdated abstract
Jain G, Sussman G, Lumry WR, Lu P, Lewis H, Maurer M. Lanadelumab improves health-related quality of life in patients with hereditary angioedema (HAE): findings from the HELP study. Allergy, asthma and clinical immunology. 2019;15.	Other; Outdated abstract
Jacobs JS, Bernstein J, Davis-Lorton M, Li HH, Soteres DF, Nurse C, et al. Increased Response to Higher Dose Lanadelumab in Hereditary Angioedema Patients: exploratory Findings From the HELP and HELP OLE Studies. Journal of allergy and clinical immunology. 2019;143(2):AB38.	Other; Outdated abstract
Gagnon R, Cicardi M, Shennak M, Zaragoza-Urdaz R, Marier JF, Lu P, et al. Lanadelumab Inhibition of plasma kallikrein activity for effective HAE prophylaxis. Allergy, Asthma and Clinical Immunology. 2019;15.	Other; Outdated abstract
Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(6):1793-802.e2.	Population
Craig T, Zuraw B, Cicardi M, Longhurst H, Feuersenger H, Prusty S, et al. LONG-TERM PROPHYLAXIS WITH SUBCUTANEOUS C1-INHIBITOR IN US PATIENTS WITH HEREDITARY ANGIOEDEMA AND VERY FREQUENT ATTACKS. Annals of allergy, asthma and immunology. 2019;123(5):S31.	Other; Outdated abstract
Craig T, Lumry W, Cicardi M, Zuraw B, Bernstein JA, Anderson J, et al. Treatment effect of switching from intravenous to subcutaneous C1-inhibitor for prevention of hereditary angioedema attacks: COMPACT subgroup findings. The journal of allergy and clinical immunology In practice. 2019;7(6):2035.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Longhurst H, Lumry W, Chiao J, Feuersenger H, Prusty S, et al. Efficacy and quality of life outcomes with long-term subcutaneous C1 inhibitor prophylaxis in the COMPACT open-label extension trial. Allergy. 2019;74:209.	Other; Outdated abstract

Citation	What is the reason for exclusion?
Cicardi M, Maurer M, Longhurst HJ, Johnston DT, Li HH, Nurse C, et al. Lanadelumab prophylaxis reduces breakthrough hereditary angioedema attacks and the need for rescue medication: exploratory findings from the phase 3 HELP study. Allergy. 2019;74:212.	Other; Outdated abstract
Chapovsky F, Hirsh J, Pawaskar D, Jacobs I, Feuersenger H. Pharmacokinetic profile of subcutaneous c1-esterase inhibitor (C1-INH [SC]) in adolescent and adult patients with hereditary angioedema (HAE). Pharmacokinetic profile of subcutaneous c1-esterase inhibitor (C1-INH [SC]) in adolescent and adult patients with hereditary angioedema (HAE). 2019;144(2).	Other; Outdated abstract
Busse PJ, Tachdjian R, Martinez-Saguer I, Lu P, Nurse C, Aygoren-Pursun E. Efficacy and safety of lanadelumab for prophylactic treatment in adolescents with hereditary angioedema (HAE). Journal of allergy and clinical immunology. 2019;143(2):AB43.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Banerji A, Manning ME, Martinez-Saguer I, Schwartz LB, Smith AM, Yang WH, et al. Subgroup Analyses From the Phase 3 HELP Study of Lanadelumab for the Prevention of Hereditary Angioedema Attacks. Journal of allergy and clinical immunology. 2019;143(2):AB42.	Other; Outdated abstract
Study to Evaluate the Efficacy and Safety of BCX7353 as an Oral Treatment for the Prevention of HAE Attacks in Japan. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dose Levels of BCX7353 as an Oral Treatment for the Prevention of Attacks in Subjects With Hereditary Angioedema. 2019.	Other; Protocol
Steiner UC, Huissoon A, Bygum A, Panovska VG, Gompels M, Cancian M, et al. Analysis of gastrointestinal (GI) symptoms in patients with hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) treated with BCX7353: results from APeX-1 Study. Allergy. 2018;73:724.	Other; Outdated abstract
Riedl MA, Tachdjian R, Schranz J, Nurse C, Bernstein JA. Consistent lanadelumab treatment effect in patients with hereditary angioedema (HAE) regardless of baseline attack frequency in the phase 3 HELP study. Journal of allergy and clinical immunology. 2018;141(2):AB47.	Other; Outdated abstract
Riedl MA, Jacobs J, Li HH, Levy DS, Chiao J, Feuersenger H, et al. Efficacy of prophylaxis with subcutaneous C1-esterase inhibitor (C1-INH [SC]) in female patients with hereditary angioedema: subgroup analysis from the COMPACT study. Allergy. 2018;73:614.	Other; Outdated abstract

Citation	What is the reason for exclusion?
Reshef A, Cicardi M, Zuraw BL, Craig T, Caballero T, Lawo JP, et al. Reduced D-dimer levels in C1-esterase-inhibitor hereditary angioedema (C1-INH-HAE) patients treated with subcutaneous C1-esterase-inhibitor (C1-INH): findings from the COMPACT study. Journal of allergy and clinical immunology Conference:. 2018;141(2 Supplement 1):AB45.	Other; Outdated abstract
Maurer M, Gierer S, Hebert J, Hao J, Lu P, Bruelle J, et al. Lanadelumab is highly efficacious at steady-state in hereditary angioedema (HAE): results of the phase 3 HELP Study. Swiss medical weekly. 2018;148:36S.	Other; Outdated abstract
Maurer M, Gierer S, Hebert J, Hao J, Lu P, Banerji A. Lanadelumab is highly efficacious at steady-state in hereditary angioedema (HAE): results of the phase 3 HELP study. Allergy. 2018;73:289.	Other; Outdated abstract
Maurer M, Davis-Lorton M, Schranz J, Hao J, Busse PJ. High responder rates in lanadelumab-treated patients in the phase 3 HELP study. Allergy. 2018;73:289.	Other; Outdated abstract
Magerl M, Rae W, Aygoren-Pursun E, Bygum A, Panovska VG, Steiner UC, et al. Prophylactic therapy with BCX7353 improves anxiety and stress in hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) patients. Allergy. 2018;73:414.	Other; Outdated abstract
Magerl M, Rae W, Aygoren-Pursun E, Bygum A, Panovska VG, Steiner UC, et al. BCX7353 improves health-related quality of life in hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE): findings from the APeX-1 study. Allergy. 2018;73:724.	Other; Outdated abstract
Lumry WR, Weller K, Magerl M, Schranz J, Jain G, Doll H, et al. Lanadelumab markedly improves health-related quality of life in hereditary angioedema patients in the HELP study. Journal of allergy and clinical immunology. 2018;141(2):AB47.	Other; Outdated abstract
Lumry WR, Weller K, Magerl M, Lu P, Jain G, Lewis H, et al. Lanadelumab markedly improves health-related quality of life in hereditary angioedema patients in the HELP study. Swiss medical weekly. 2018;148:28S.	Other; Outdated abstract
Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema. Journal of Allergy and Clinical Immunology: In Practice. 2018;6(5):1733-41.e3.	Outcome
Longhurst H, Lumry W, Weller K, Magerl M, Lu P, Jain G, et al. Lanadelumab improves health-related quality of life in patients with hereditary Angioedema (HAE): findings from the HELP study. Clinical and experimental allergy Conference:. 2018;48(11):1524.	Other; Outdated abstract

Citation	What is the reason for exclusion?
Li HH, Riedl MA, Craig T, Longhurst HJ, Cicardi M, Zuraw BL, et al. Initiation of Prophylactic Treatment with Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) for Prevention of Hereditary Angioedema (HAE) Attacks and Onset of Effect: findings from the Phase III COMPACT Study. Initiation of Prophylactic Treatment with Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) for Prevention of Hereditary Angioedema (HAE) Attacks and Onset of Effect: findings from the Phase III COMPACT Study. 2018;141(2):AB45.	Other; Outdated abstract
Li HH, Feuersenger H, Chiao J, Machnig T, Jacobs I. Long-term treatment experience with subcutaneous C1-esterase inhibitor for the prevention of hae attacks: 2-year efficacy results from the us compact open-label extension study. Allergy and asthma proceedings. 2018;39(5):401.	Other; Outdated abstract
Levy DS, Chiao J, Feuersenger H, Craig T, Longhurst HJ, Cicardi M, et al. Prevention of Attacks of Hereditary Angioedema (HAE) with Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) by Anatomical Location: results From the Phase III COMPACT Study (NCT01912456). Prevention of Attacks of Hereditary Angioedema (HAE) with Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) by Anatomical Location: results From the Phase III COMPACT Study (NCT01912456). 2018;141(2):AB45.	Other; Outdated abstract
Johnston DT, Anderson JT, Schranz J, Nurse C, Cicardi M. Efficacy of lanadelumab in patients switching from long-term prophylaxis with C1-inhibitor (C1-INH): results from the phase 3 HELP Study. Journal of allergy and clinical immunology. 2018;141(2):AB47.	Other; Outdated abstract
Gower RG, Li H, Levy D, Jacobs I. Patients with severe hereditary angioedema treated with subcutaneous C1-esterase inhibitor (C1-INH [SC]) to reduce the incidence and severity of attacks: results from a phase 3 trial. Pediatrics. 2018;142(1).	Other; Outdated abstract
Farkas H, Aygoren-Pursun E, Panovska VG, Huissoon A, Kinaciyan T, Murray S, et al. RELATIONSHIP OF TARGET CONCENTRATIONS WITH EFFICACY: RESULTS FROM THE APEX-1 STUDY OF BCX7353. Annals of allergy, asthma and immunology Conference:. 2018;121(5 Supplement):S33.	Other; Outdated abstract
Bygum A, Panovska VG, Maurer M, Magerl M, Farkas H, Cicardi M, et al. Pharmacokinetic (PK) and Pharmacodynamic (PD) effects of BCX7353 in patients with hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE): results from APeX-1 study. Allergy. 2018;73:723.	Outcome
Bernstein JA, Banerji A, Schranz J, Nurse C, Riedl M, Lu P. Lanadelumab reduces high morbidity attacks in patients with hereditary angioedema (HAE): results from the phase 3 HELP study. Allergy. 2018;73:288.	Other; Outdated abstract
A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema. A Phase 3,	Other; Protocol

Citation	What is the reason for exclusion?
randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema - Evaluate study between two doses levels of BCX7353 and placebo for prevention of attacks in subjects with hereditary angioedema. 2018.	
A clinical trial to assess 2 different doses of BCX7353 compared to placebo as an oral treatment for the prevention of attacks in people with HAE. A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema - APEX-2. 2018.	Other; Protocol
A Study to Investigate CSL312 in Subjects With Hereditary Angioedema (HAE). A Multicenter, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema. 2018.	Other; Protocol
Efficacy and Safety Study of BCX7353 as an Oral Treatment for the Prevention of Attacks in HAE. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Two Dose Levels of BCX7353 as an Oral Treatment for the Prevention of Attacks in Subjects With Hereditary Angioedema. 2018.	Other; Protocol
Wang Y, Martin P, Lu P, Schranz J. Pharmacokinetics (PK) and pharmacodynamics (PD) of c1 esterase inhibitor (c1-IHN) for prophylaxis of angioedema attacks in patients (PTS) with hereditary angioedema (HAE). Pharmacokinetics (PK) and pharmacodynamics (PD) of c1 esterase inhibitor (c1-IHN) for prophylaxis of angioedema attacks in patients (PTS) with hereditary angioedema (HAE). 2017;Conference: 36th Annual Congress of the European Academy of Allergy and Clinical Immunology, EAACI 2017. Finland. 72(pp 148).	Other; Outdated abstract
Tarzi M, Cicardi M, Zuraw B, Craig T, Longhurst H, Caballero T, et al. Prevention of Hereditary Angioedema (HAE) attacks with subcutaneous C1-INH (SC) preparation of CSL830 in the COMPACT study: effects on severity and attack location. Allergy. 2017;72:597.	Other; Outdated abstract
Lumry WR, Craig T, Cicardi M, Zuraw BL, Longhurst H, Farkas H, et al. Can routine prophylactic subcutaneous C1-inhibitor [C1-INH(SC)] alleviate psychological and physical disabilities caused by HAE? Findings from the COMPACT study (NCT01912456). Allergy, asthma and clinical immunology. 2017;13.	Outcome
Longhurst HJ, Li HH, Riedl MA, Craig TJ, Reshef A, Farkas H, et al. Subcutaneous C1-Esterase Inhibitor to Prevent Hereditary Angioedema (HAE) Attacks: subject and investigator assessments from the compact trial. Journal of allergy and clinical immunology. 2017;139(2):AB234.	Other; Outdated abstract

Citation	What is the reason for exclusion?
Longhurst H, Cicardi M, Zuraw B, Craig T, Caballero T, Farkas H, et al. Subcutaneous C1-INH (SC) preparation (CSL830) in the prevention of Hereditary Angioedema (HAE) attacks: first findings from the COMPACT extension study. Allergy. 2017;72:100.	Other; Outdated abstract
Gurmen ES, Dogan S, Sert E, Dikmetas C, Hussein S. Effect of C1 esterase inhibitor in hereditary angioedema treatment. The American journal of emergency medicine. 2017;35(6):942.e5-.e6.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Zuraw B, Lumry W, Bernstein J, Cicardi M, Anderson J, et al. Preventive effect of subcutaneous C1 inhibitor in patients with very frequent attacks of hereditary angioedema. Annals of allergy, asthma and immunology. 2017;119(5):S4.	Other; Outdated abstract
Bernstein JA, Henry Li H, Craig TJ, Longhurst HJ, Farkas H, Manning ME, et al. Placebo-controlled trials of C1-Inhibitor (C1-INH) replacement therapy for routine prevention of attacks in patients with hereditary angioedema (HAE). Journal of allergy and clinical immunology. 2017;139(2):AB234.	Other; Outdated abstract
Banerji A, Riedl M, Bernstein J, Cicardi M, Longhurst H, Zuraw B, et al. Lanadelumab for prevention of attacks in hereditary angioedema: results from the phase 3 help study. Annals of allergy, asthma and immunology. 2017;119(5):S5.	Other; Outdated abstract
Aygoren-Pursun E, Steiner U, Panovska VG, Farkas H, Rae W, Aberer W, et al. BCX7353, a once-daily oral kallikrein inhibitor, is effective and safe in the prophylaxis of acute attacks in patients with hereditary angioedema: results from the first interim analysis of the APeX-1 study. Allergy, asthma and clinical immunology. 2017;13.	Other; Outdated abstract
Aygoren E, Bygum A, Steiner U, Magerl M, Grivcheva Panovska V, Farkas H, et al. BCX7353, a once-daily oral kallikrein inhibitor, is effective and safe in the prophylaxis of acute attacks in patients with hereditary angioedema: attack-level analysis of the APeX-1 study. Allergy. 2017;72:584.	Other; Outdated abstract
Long Term Safety Study of BCX7353 in HAE. An Open-Label study to Evaluate the Long-Term Safety of Daily Oral BCX7353 in subjects with Type I and II Hereditary Angioedema. 2017.	Other; Protocol
A study in patients to assess the effectiveness, safety and patient tolerability of different doses of BCX7353 to treat acute HAE attacks compared to placebo. A randomized, double-blind, placebo-controlled, dose-ranging, study to evaluate the efficacy, safety and tolerability of single doses of BCX7353 as an acute attack treatment in subjects with hereditary angioedema. 2017.	Other; Protocol
Caballero T, Maurer M, Longhurst HJ, Aberer W, Bouillet L, Fabien V, et al. Triggers and Prodromal Symptoms of Angioedema Attacks in Patients With Hereditary	Study design (non-RCT,

Citation	What is the reason for exclusion?
Angioedema. Journal of investigational allergology & clinical immunology. 2016;26(6):383-6.	opinion, commentary, single-arm, etc)
BCX7353 for the prevention of HAE attacks. A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema. 2016.	Other; Protocol
Zuraw BL, Cicardi M, Longhurst HJ, Bernstein JA, Li HH, Magerl M, et al. Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70(10):1319-28.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Aabom A, Andersen KE, Perez-Fernandez E, Caballero T, Bygum A. Health-related quality of life in Danish patients with hereditary angioedema. Acta dermato-venereologica. 2015;95(2):225-6.	Study design (non-RCT, opinion, commentary, single-arm, etc)
A placebo controlled trial of of three doses of BCX7353 to evaluate the safety and efficacy in the prevention of attacks in patients with HAE. A randomized, double-blind, 4 week, placebo-controlled, dose-ranging, parallel-group study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema. 2015.	Other; Protocol
Study to determine the efficacy and safety of C1 Esterase Inhibitor liquid for injection compared to placebo in the prevention of Angioedema attacks in adolescents and adults with hereditary angioedema. A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults with Hereditary Angioedema. 2015.	Other; Protocol
Efficacy and safety study to evaluate DX-2930 in preventing agioedema attacks in patients with Type I and Type II heriditary angioedema (HAE). HELP Study™: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX 2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). 2015.	Other; Protocol

Citation	What is the reason for exclusion?
Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE. HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE). 2015.	Other; Protocol
Study to Evaluate the Clinical Efficacy and Safety of Subcutaneously Administered C1 Esterase Inhibitor for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema. A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema. 2015.	Other; Protocol
Zuraw B, Craig T, Longhurst H, Martinez-Saguer I, Li H, Bernstein J, et al. Dose-ranging trial of a volume-reduced, subcutaneous formulation of a C1-INH concentrate (CSL830) for the prevention of acute attacks of hereditary angioedema. Allergy. 2014;69:52.	Other; Outdated abstract
Pedrosa M, Lobera T, Panizo C, Jurado J, Caballero T. Long-term prophylaxis with C1-inhibitor concentrate in patients with hereditary angioedema. Journal of investigational allergology & clinical immunology. 2014;24(4):271-3.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Martinez-Saguer I, Cicardi M, Suffritti C, Rusicke E, Aygoren-Pursun E, Stoll H, et al. Pharmacokinetics of plasma-derived C1-esterase inhibitor after subcutaneous versus intravenous administration in subjects with mild or moderate hereditary angioedema: The PASSION study. Transfusion. 2014;54(6):1552-61.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Lumry WR, Miller DP, Newcomer S, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy and Asthma Proceedings. 2014;35(5):371-6.	Outcome
Lumry WR, Miller DP, Beusterien K, Hautamaki E, Fitts D, Dayno J. Health-related quality of life (HRQoL) in patients with hereditary angioedema (HAE) receiving nanofiltered C1 inhibitor (C1 INH-nf) for prophylaxis: results of a randomised, placebo-controlled, cross-over study. Allergy. 2014;69:491.	Other; Outdated abstract
Dayno J, Miller DP, Hautamaki E, Newcomer S, Fitts D, Lumry WR. Relationship between angioedema attacks and health-related quality of life outcomes in patients with hereditary angioedema (HAE). Journal of allergy and clinical immunology. 2014;133(2 SUPPL. 1):AB33.	Outcome

Citation	What is the reason for exclusion?
Rizk C, Karsh J, Santucci S, Yang W. Self-administration of intravenous C1 esterase inhibitor in hereditary angioedema. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(9):791-2.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Riedl MA, Lumry WR, Li HH, Craig TJ, Fitts D, Kalfus I, et al. Nanofiltered C1 esterase inhibitor for treatment of laryngeal attacks in patients with hereditary angioedema. American Journal of Rhinology and Allergy. 2013;27(6):517-21.	Intervention/Comparator
Lumry WR, Miller DP, Beusterien K, Hautamaki E, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving nanofiltered C1 inhibitor for prophylaxis: results of a randomized, placebocontrolled cross-over study. Annals of allergy, asthma and immunology. 2013;111(5 SUPPL. 1):A105.	Other; Outdated abstract
Kawalec P, Holko P, Paszulewicz A, Obtulowicz K. Administration of conestat alfa, human C1 esterase inhibitor and icatibant in the treatment of acute angioedema attacks in adults with hereditary angioedema due to C1 esterase inhibitor deficiency. Treatment comparison based on systematic review results. Pneumonologia i Alergologia Polska. 2013;81(2):95-104.	Non-English
Farkas H, Csuka D, Zotter Z, Szabo E, Czaller I, Varga L, et al. Treatment of attacks with plasma-derived C1-inhibitor concentrate in pediatric hereditary angioedema patients. The Journal of allergy and clinical immunology. 2013;131(3):909-11.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig TJ, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. Annals of Allergy, Asthma and Immunology. 2013;111(3):211-5.	Population
Bork K, Steffensen I, Machnig T. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: A systematic literature review. Allergy and Asthma Proceedings. 2013;34(4):312-27.	On topic SLR/MA/NMA
A Study to Evaluate the Clinical Efficacy and Safety of Subcutaneously Administered C1-esterase Inhibitor in the Prevention of Hereditary Angioedema. A Double-blind, Randomized, Placebo-controlled, Cross-over Study to Evaluate the Clinical Efficacy and Safety of Subcutaneous Administration of Human Plasma-derived C1-esterase Inhibitor in the Prophylactic Treatment of Hereditary Angioedema. 2013.	Other; Protocol
Riedl MA, Hurewitz DS, Levy R, Busse PJ, Fitts D, Kalfus I. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: An open-label trial. Annals of Allergy, Asthma and Immunology. 2012;108(1):49-53.	Population

Citation	What is the reason for exclusion?
Costantino G, Casazza G, Bossi I, Duca P, Cicardi M. Long-term prophylaxis in hereditary angio-oedema: A systematic review. BMJ Open. 2012;2(4):e000524.	On topic SLR/MA/NMA
Martinez-Saguer I, Cicardi M, Aygoren-Pursun E, Rusicke E, Klingebiel T, Kreuz W. Pharmacokinetics of plasma-derived C1-esterase inhibitor after subcutaneous versus intravenous administration in subjects with moderate hereditary angioedema. Allergy. 2011;66:423.	Other; Outdated abstract
Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. New England Journal of Medicine. 2010;363(6):513-22.	Population
Schlenger R. Prefilled syringe instead of infusion - The hereditary angioedema under control. Klinikarzt. 2010;39(12):579.	Non-English
Vernon MK, Rentz AM, Wyrwich KW, White MV, Grienenberger A. Psychometric validation of two patient-reported outcome measures to assess symptom severity and changes in symptoms in hereditary angioedema. Quality of Life Research. 2009;18(7):929-39.	Population
Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. New England Journal of Medicine. 1996;334(25):1630-4.	Outcome
Brickman CM, Hosea SW. Hereditary angioedema. International journal of dermatology. 1983;22(3):141-7.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Agostoni A. The management of hereditary angioedema. La Ricerca in clinica e in laboratorio. 1983;13(1):55-9.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Frank MM. The C1 esterase inhibitor and hereditary angioedema. Journal of clinical immunology. 1982;2(2):65-8.	Study design (non-RCT, opinion, commentary, single-arm, etc)

Citation	What is the reason for exclusion?
Sacca JD. Hereditary angioedema (HAE). Annals of allergy. 1979;42(2):88-90.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Calvert GD, Kilpatrick D, McQueen EG, Houston IB, Kilpatrick JA, Veale AM. Hereditary angioneurotic oedema. The New Zealand medical journal. 1973;78(501):337-42.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Brackertz D, Kueppers F. Hereditary angioneurotic oedema. Lancet (London, England). 1973;2(7830):680.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Brackertz D, Kueppers F. Possible therapy in hereditary angioneurotic edema (HAE). Klinische Wochenschrift. 1973;51(12):620-2.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Bedford S. Hereditary angio-oedema. Proceedings of the Royal Society of Medicine. 1971;64(10):1049-50.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Rosen FS, Austen KF. The "neurotic edema" (hereditary angioedema). The New England journal of medicine. 1969;280(24):1356-7.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Juhlin L, Michaelsson G. Use of a kallikrein inhibitor in the treatment of urticaria and hereditary angioneurotic edema. Acta dermato-venereologica. 1969;49(1):37-44.	Study design (non-RCT, opinion, commentary,

Citation	What is the reason for exclusion?
	single-arm, etc)
Date of the search: 16 Sept 2024	
Riedl MA, Soteres D, Sublett JW, Desai B, Tomita D, Collis P, et al. Hereditary angioedema outcomes in US patients switched from injectable long-term prophylactic medication to oral berotralstat. Annals of Allergy, Asthma and Immunology. 2024;132(4):505-11.e1.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Longhurst HJ, Bouillet L, Cancian M, Grivcheva-Panovska V, Koleilat M, Magerl M, et al. Hereditary angioedema attacks in patients receiving long-term prophylaxis: a systematic review. Allergy and Asthma Proceedings. 2024;45(3):213.	Incomplete/Insufficient/Partial data
Kiani-Alikhan S, Gower R, Craig T, Wedner HJ, Kinaciyan T, Aygoren-Pursun E, et al. Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial. Journal of Allergy and Clinical Immunology: In Practice. 2024;12(3):733-43.e10.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Jacobs J, Magerl M, Martinez-Saguer I, Li H, Bernstein J, Hsu C, et al. Garadacimab For Hereditary Angioedema Prophylaxis In Adolescents: Efficacy And Safety From The Phase 3 (VANGUARD) Study And Open-Label Extension (Second Interim Analysis). Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB6.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Tachdjian R, Bernstein JA, Anderson J, Nurse C, Watt M, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab in adolescents. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2024.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Craig T, Anderson J, Jacobs J, Tachdjian R, Farkas H, Yang W, et al. Integrated Safety And Efficacy Of Garadacimab For Hereditary Angioedema Prophylaxis Across 3 Clinical Trials: Phase 2, Pivotal Phase 3, And Open-Label Extension Studies. Journal of Allergy and Clinical Immunology. 2024;153(2):AB256.	Study design (non-RCT, opinion, commentary, single-arm, etc)

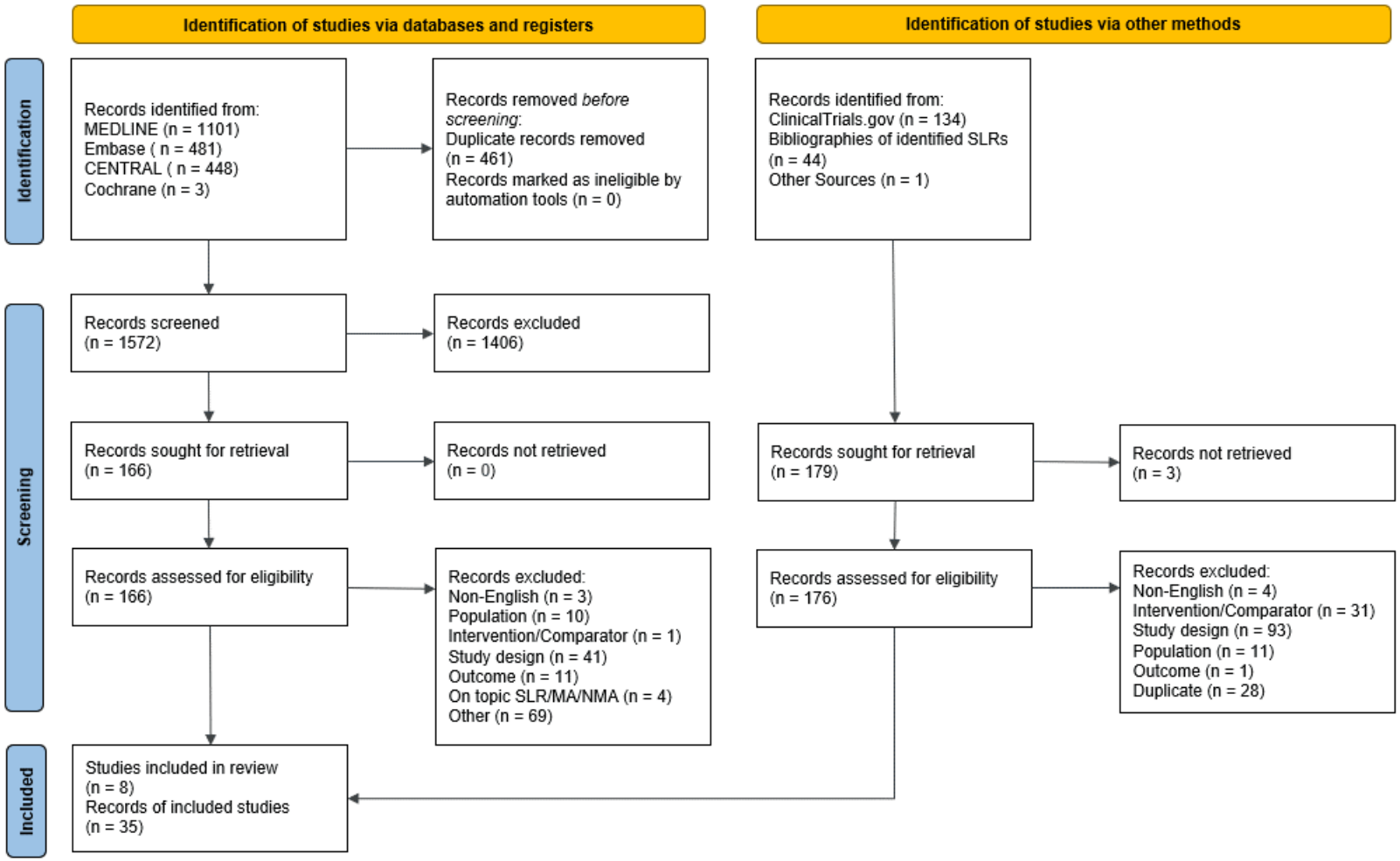
Citation	What is the reason for exclusion?
Anderson J, Levy D, Sussman G, Jacobs J, Farkas H, Pollen M, et al. Long-term safety and efficacy with garadacimab for hereditary angioedema prophylaxis in an open-label extension study. Allergy and Asthma Proceedings. 2024;45(3):212.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Study of IV Human Plasma-derived C1 Esterase Inhibitor Concentrate in Patients With Congenital C1-INH Deficiency for Treatment and Pre-procedure Preventing of Acute Hereditary Angioedema Attacks. Prospective, Multicenter, Randomized, Double-blind, Parallel Group, Placebo- Controlled, Efficacy and Safety Phase 3 Study of an Intravenous Human Plasma- Derived C1 Esterase Inhibitor (C1-INH) Concentrate in Participants With Congenital C1-INH Deficiency for the Treatment and Pre-procedure Prevention of Acute Hereditary Angioedema Attacks. 2024.	Incomplete/Insufficient/Partial data
Watt M, Malmenas M, Romanus D, Haeussler K. Network meta-analysis for indirect comparison of lanadelumab and berotralstat for the treatment of hereditary angioedema. Journal of Comparative Effectiveness Research. 2023;12(6):e220188.	On topic SLR/MA/NMA
Peter JG, Desai B, Tomita D, Collis P, Stobiecki M. Assessment of HAE prophylaxis transition from androgen therapy to berotralstat: A subset analysis of the APeX-S trial. World Allergy Organization Journal. 2023;16(11):100841.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Mansour E, Bernstein J, Riedl M, Kiani S, Aygoren-Pursun E, Choudhry Z, et al. Lanadelumab safety and efficacy in hereditary angioedema after switching from prior long-term prophylaxis: analysis from the HELP OLE study. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):12.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Lumry WR, Maurer M, Weller K, Riedl MA, Watt M, Yu M, et al. Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. Annals of Allergy, Asthma and Immunology. 2023;131(1):101-8.e3.	Study design (non-RCT, opinion, commentary, single-arm, etc)
Aygoren-Pursun E, Manning M, Fain O, Desai B, Tomita D, Johnston D, et al. Long-term HAE Prophylaxis with Berotralstat Is Well Tolerated and Effective: Analysis for the APeX-S Study. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB129.	Study design (non-RCT, opinion, commentary,

Citation	What is the reason for exclusion?
	single-arm, etc)
Department of Error. Erratum: department of Error (The Lancet (2023) 401(10382) (1079–1090), (S0140673623003501), (101016/S0140-6736(23)00350-1)). 2023;401(10384):1266.	Duplicate
Prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety phase 3 study of an intravenous human plasma-derived C1 esterase inhibitor (C1-INH) concentrate in participants with congenital C1-INH deficiency for the treatment and pre-procedure prevention of acute hereditary angioedema attacks. Prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety phase 3 study of an intravenous human plasma-derived C1 esterase inhibitor (C1-INH) concentrate in participants with congenital C1-INH deficiency for the treatment and pre-procedure prevention of acute hereditary angioedema attacks - CONE-02. 2023.	Population
Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database of Systematic Reviews. 2022;2022(11):CD013403.	On topic SLR/MA/NMA

Abbreviations: MA = meta-analysis; NMA = network meta-analysis; SLR = systematic literature review; RCT = randomized controlled trial

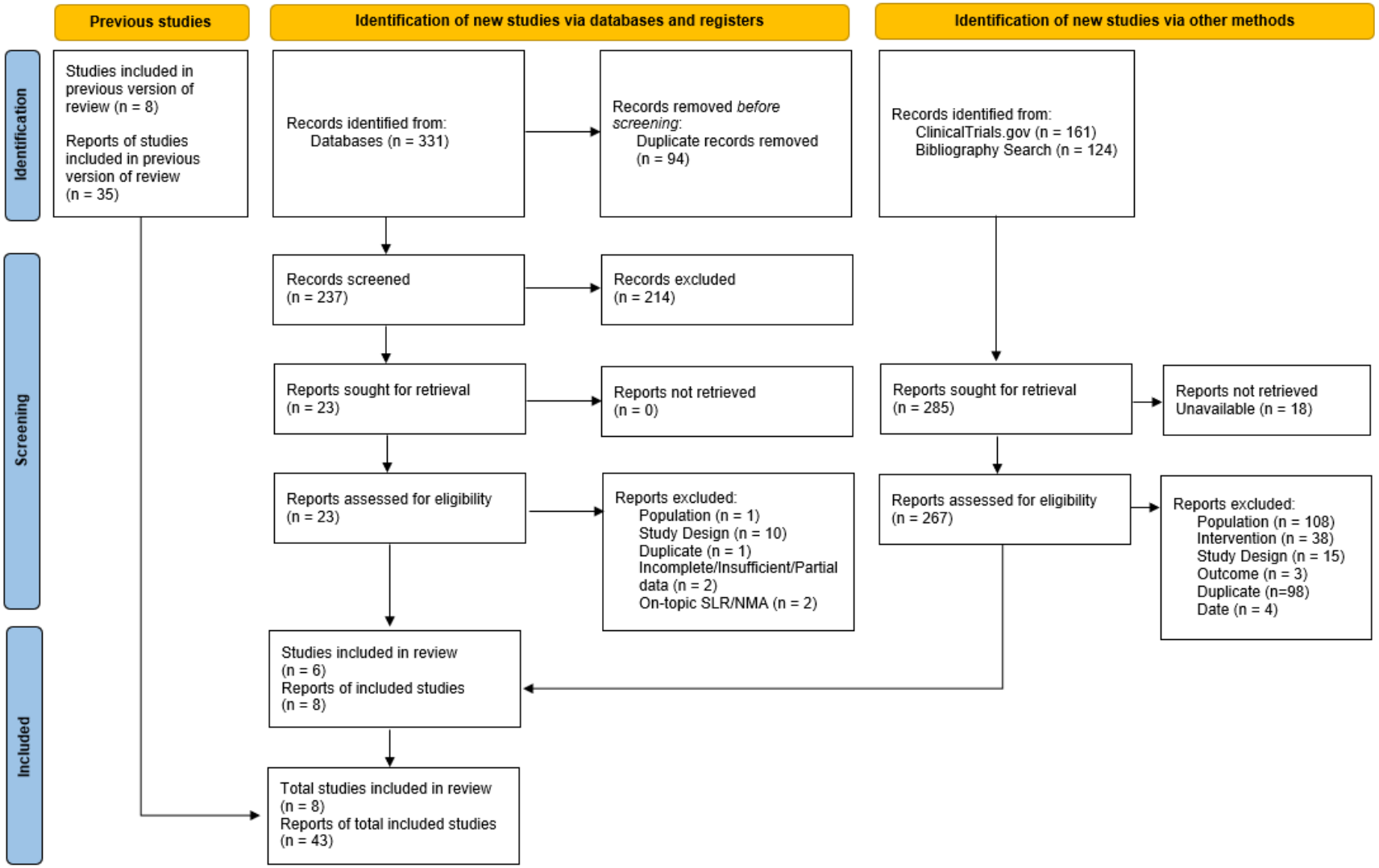
Appendix B: PRISMA Diagrams

Supplementary Figure 1: PRISMA flow diagram (August 2022)



Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NMA = network meta-analysis; RCT = randomized controlled trial; SLR = systematic literature review.
Source: Page et al., 2021.

Supplementary Figure 2: SLR Update PRISMA flow diagram (September 2024)



Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NMA = network meta-analysis; RCT = randomized controlled trial; SLR = systematic literature review.
Source: Page et al., 2021.

Appendix C: Study Quality Assessment

Supplementary Table 5: Assessment of Study Quality

Trial; NCT	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and the outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
VANGUARD NCT04656418	YES	YES	YES	YES	NO	NO	YES
APeX-1 NCT02870972	YES	YES	NO	YES	NO	NO	YES
APeX-2 NCT03485911	YES	YES	YES	YES	NO	NO	YES
APeX-J NCT03873116	YES	YES	YES	YES	NO	NO	YES
COMPACT NCT01912456	YES	YES	YES	YES	NO	NO	YES
COMPACT OLE NCT02316353	YES	NO	YES	NO	NO	NO	YES
HELP NCT02586805	YES	YES	YES	YES	NO	NO	YES
NA NCT03712228	YES	YES	NO	YES	NO	NO	YES

Abbreviations: ITT = intent to treat; NA = not available; OLE = open-label extension

Appendix D: Feasibility Assessment

Heterogeneity in study design was observed in the COMPACT, COMPACT OLE, phase 2 garadacimab, and APeX-J trials. The COMPACT trial was a cross-over study where patients received one of four treatment sequences during two treatment periods up to 16 weeks each. Using publicly available post-crossover data from COMPACT would introduce significant heterogeneity into potential analyses; therefore, to mitigate this limitation, pre-crossover data collected at 16 weeks was provided directly by the trial sponsor (CSL Behring) and were deemed more appropriate for inclusion in the analyses.

In addition, COMPACT open-label extension (OLE) study was excluded from the feasibility assessment due to heterogeneity in study design. The COMPACT OLE was a parallel-arm study of patients who completed the placebo-controlled COMPACT trial in addition to subcutaneous C1-INH-naive patients. Given that only pre-crossover COMPACT trial data was included in the analyses, the COMPACT OLE study was excluded as it encompassed post-crossover patients from the parent trial.

The phase 2 garadacimab study design included two treatment periods: treatment period 1 (12 weeks) was randomized, double-blind and placebo-controlled, while treatment period 2 (≥44-week) was a randomized OLE. At the beginning of the OLE, patients were re-randomized (if receiving placebo, garadacimab 75 mg, or garadacimab 400 mg) or continued to receive garadacimab 200 mg or garadacimab 600 mg once monthly. Despite being randomized, the OLE phase was not placebo-controlled and its data were excluded from the analyses.

Lastly, data from Parts 2 and 3 of the APeX-J trial would also introduce significant heterogeneity into potential analyses. Part 1 was a randomized, placebo-controlled phase of berotralstat 150 or 110 mg (24 weeks). Part 2 was a dose-blinded phase in which berotralstat-treated patients continued the same dose and placebo patients were re-randomized to berotralstat 150 or 110 mg (28 weeks). In Part 3, the remaining patients received berotralstat 150 mg in an open-label extension (≥52 weeks). Data from Parts 2 and 3 of the study were excluded from the analyses due to the lack of a placebo arm and the open-label design.

Appendix E: Model Diagnostics

Supplementary Table 6: Model diagnostics for time-normalized number of HAE attacks during treatment

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	113.55	29.07	-
	Random effects	97.6	13.15	1.435 (0.366 to 4.508)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: DIC = deviance information criterion; HAE = hereditary angioedema; SD = standard deviation

Supplementary Table 7: Model diagnostics for time-normalized number of HAE attacks treated with on-demand therapy

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	115.11	33.61	-
	Random effects	94.47	13.08	1.814 (0.508 to 4.683)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: DIC = deviance information criterion; HAE = hereditary angioedema; SD = standard deviation

Supplementary Table 8: Model diagnostics for time-normalized number of moderate and/or severe HAE attacks during treatment

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	95.41	18.26	-
	Random effects	90.51	13.38	1.239 (0.12 to 4.436)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: DIC = deviance information criterion; HAE = hereditary angioedema; SD = standard deviation

Supplementary Table 9: Model diagnostics for proportion of attack-free patients

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	29.82	10.04	-
	Random effects	30.3	10.31	0.86 (0.04 to 1.93)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: CrI = credible interval; DIC = deviance information criterion; SD = standard deviation

Supplementary Table 10: Model diagnostics for TEAEs

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	10.44	10.16	-
	Random effects	11.39	10.63	0.66 (0.03 to 1.9)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: CrI = credible interval; DIC = deviance information criterion; SD = standard deviation; TEAEs = treatment-emergent adverse events

Supplementary Table 11: Model diagnostics for change from baseline in AE-QoL total score

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Consistency	Fixed effect	58.34	9.92	-
	Random effects	58.19	9.87	1.02 (0.06 to 1.95)

[a] A difference in the DIC between the models of more than ±3 was considered meaningful (Dias et al., 2018).

- Dias S, Ades AE, Welton NJ et al. Network Meta-Analyses for Decision-Making. 2018. John Wiley & Sons: Hoboken, NJ.
- Dias S, Welton NJ, Sutton AJ et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: https://nicedsu.sites.sheffield.ac.uk/.

Abbreviations: AE-QoL = angioedema quality of life; CrI = credible interval; DIC = deviance information criterion; SD = standard deviation

Appendix F: Random-effects Results

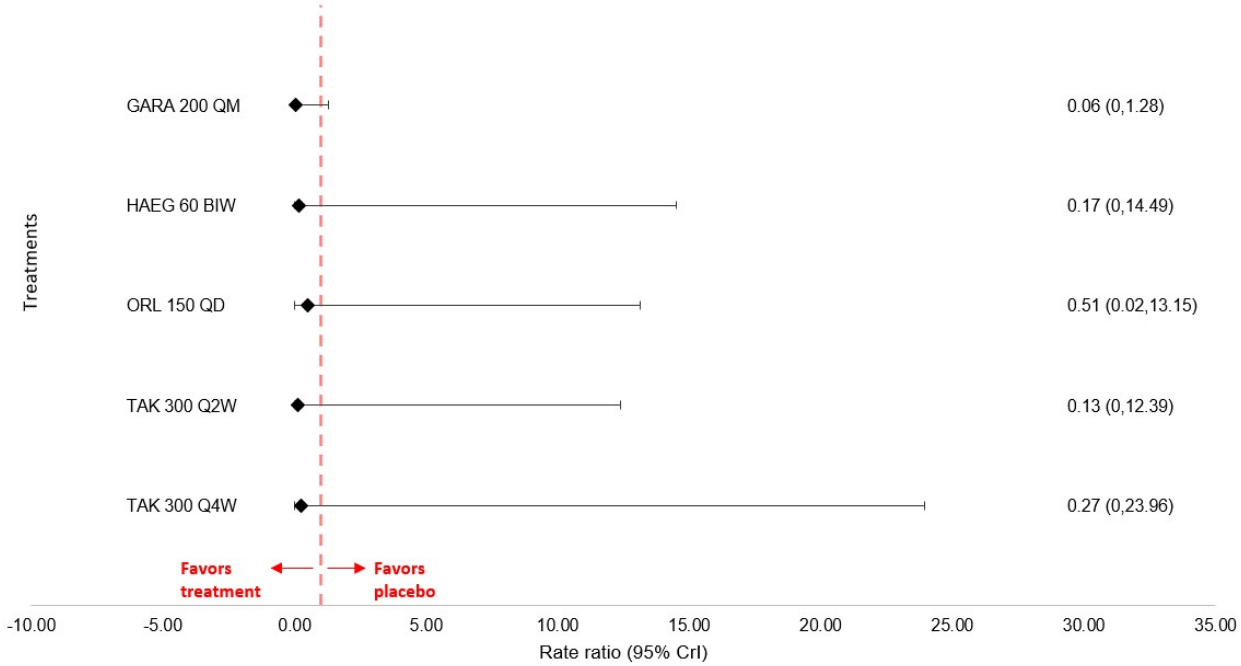
Supplementary Figure 3: League table for random effects NMA of time-normalized number of HAE attacks during treatment

GARA 200 QM					
0.47 (0.00 to 98.95)	TAK 300 Q2W				
0.36 (0.00 to 75.97)	0.76 (0.00 to 480.52)	HAEG 60 BIW			
0.23 (0.00 to 47.30)	0.49 (0.01 to 40.95)	0.63 (0.00 to 335.74)	TAK 300 Q4W		
0.12 (0.00 to 9.56)	0.26 (0.00 to 62.93)	0.33 (0.00 to 77.78)	0.52 (0.00 to 134.89)	ORL 150 QD	
0.06 (0.00 to 1.28)	0.13 (0.00 to 12.39)	0.17 (0.00 to 14.49)	0.27 (0.00 to 23.96)	0.51 (0.02 to 13.15)	PBO

Note: Values are RRs (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: RR < 1 implies that column is better than row
Note: Pink squares are statistically significant

Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; RR = rate ratio; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 4: Forest plot (active treatments vs. PBO) for random effects NMA of time-normalized number of HAE attacks during treatment



Abbreviations: C1INH = C1 esterase inhibitor; CrI = credible interval; Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Table 12: Random effects p-best and SUCRA scores for time-normalized number of HAE attacks during treatment

Treatment	Probability Best (%)	SUCRA (%)
PBO	0	14
GARA 200 QM	52	83
HAEG 60 BIW	16	58
ORL 150 QD	3	33
TAK 300 Q2W	20	65
TAK 300 Q4W	8	47

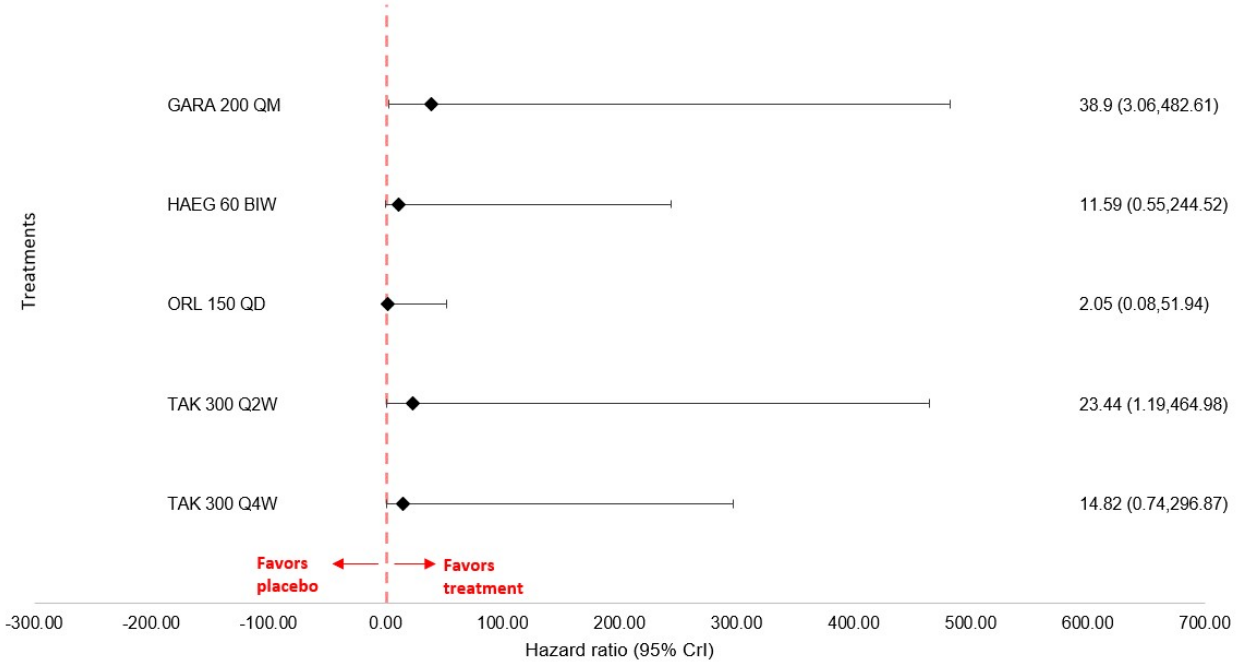
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; SUCRA = Surface Under the Cumulative Ranking curve; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 5: League table for random effects NMA of proportion of attack-free patients

GARA 200 QM					
1.66 (0.03 to 82.46)	TAK 300 Q2W				
2.61 (0.05 to 131.16)	1.58 (0.14 to 18.38)	TAK 300 Q4W			
3.4 (0.06 to 171.19)	2.04 (0.03 to 145.07)	1.29 (0.02 to 91.63)	HAEG 60 BIW		
18.95 (0.3 to 1175.56)	11.39 (0.15 to 927.6)	7.2 (0.09 to 599.98)	5.61 (0.07 to 497.95)	ORL 150 QD	
38.9 (3.06 to 482.61)	23.44 (1.19 to 464.98)	14.82 (0.74 to 296.87)	11.59 (0.55 to 244.52)	2.05 (0.08 to 51.94)	PBO

Note: Values are HRs (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: HR > 1 implies that column is better than row
Note: Pink squares are statistically significant
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; HR = hazard ratio; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 6: Forest plot (active treatments vs. PBO) for random effects NMA of proportion of attack-free patients



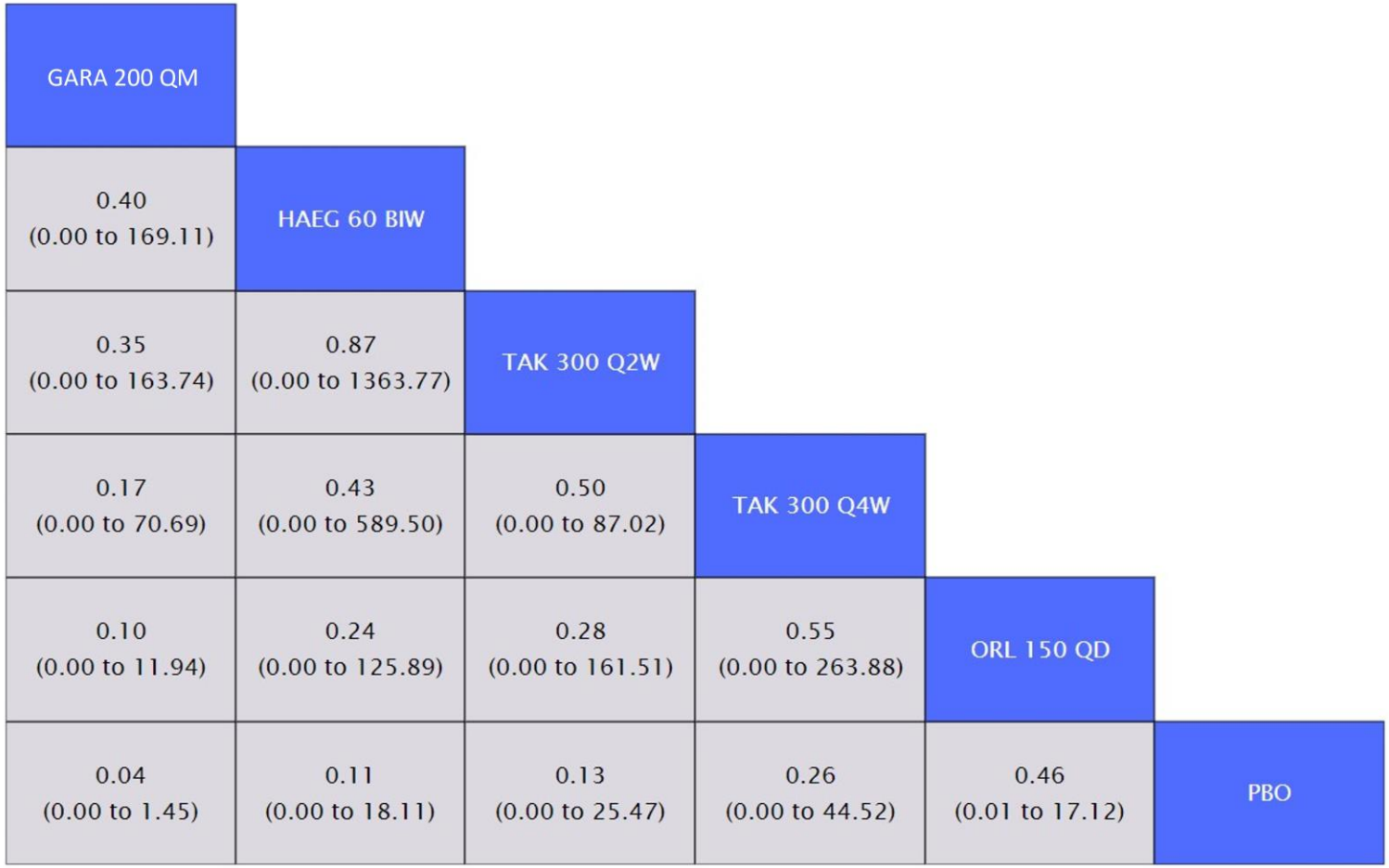
Abbreviations: C1INH = C1 esterase inhibitor; CrI = credible interval; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Table 13: Random effects p-best and SUCRA scores for proportion of attack-free patients

Treatment	Probability Best (%)	SUCRA (%)
PBO	0	9
GARA 200 QM	47	79
HAEG 60 BIW	15	56
ORL 150 QD	2	25
TAK 300 Q2W	25	72
TAK 300 Q4W	10	59

Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; SUCRA = Surface Under the Cumulative Ranking curve; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

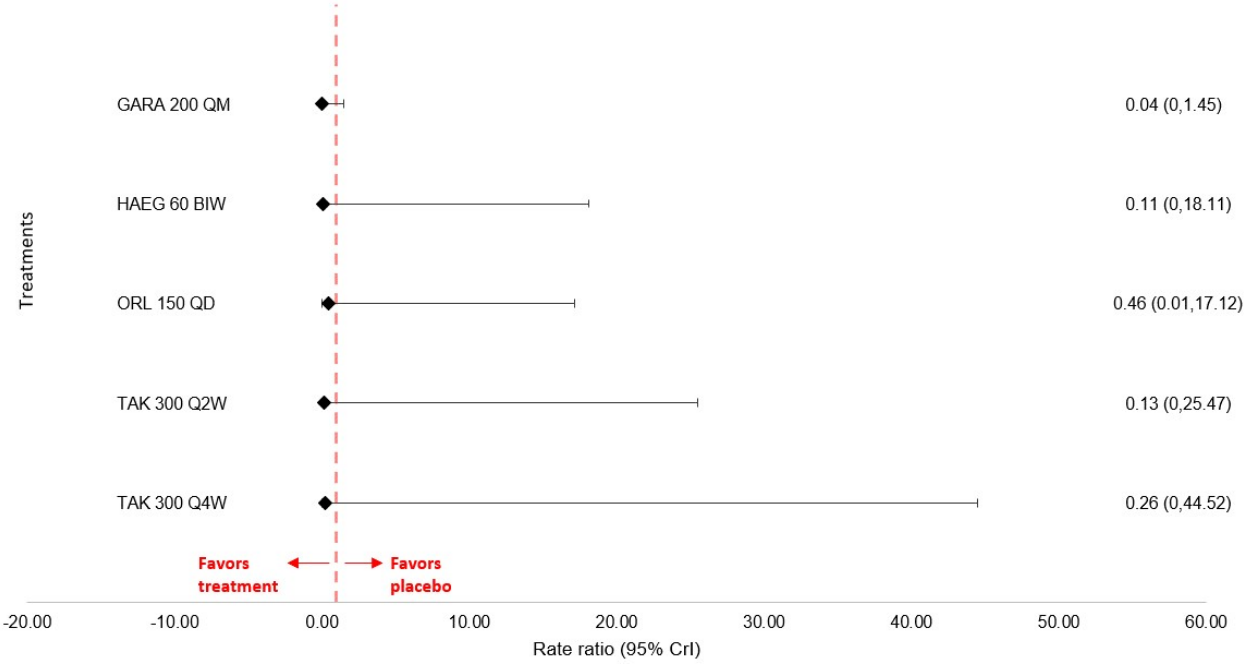
Supplementary Figure 7: League table for random effects NMA of time-normalized number of HAE attacks treated with on-demand therapy



Note: Values are RRs (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: RR < 1 implies that column is better than row
Note: Pink squares are statistically significant

Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; RR = rate ratio; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 8: Forest plot (active treatments vs. PBO) for random effects NMA of time-normalized number of HAE attacks treated with on-demand therapy



Abbreviations: C1INH = C1 esterase inhibitor; CrI = credible interval; Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Table 14: Random effects p-best and SUCRA scores for time-normalized number of HAE attacks treated with on-demand therapy

Treatment	Probability Best (%)	SUCRA (%)
PBO	0	15
GARA 200 QM	48	81
HAEG 60 BIW	22	62
ORL 150 QD	3	35
TAK 300 Q2W	18	61
TAK 300 Q4W	8	46

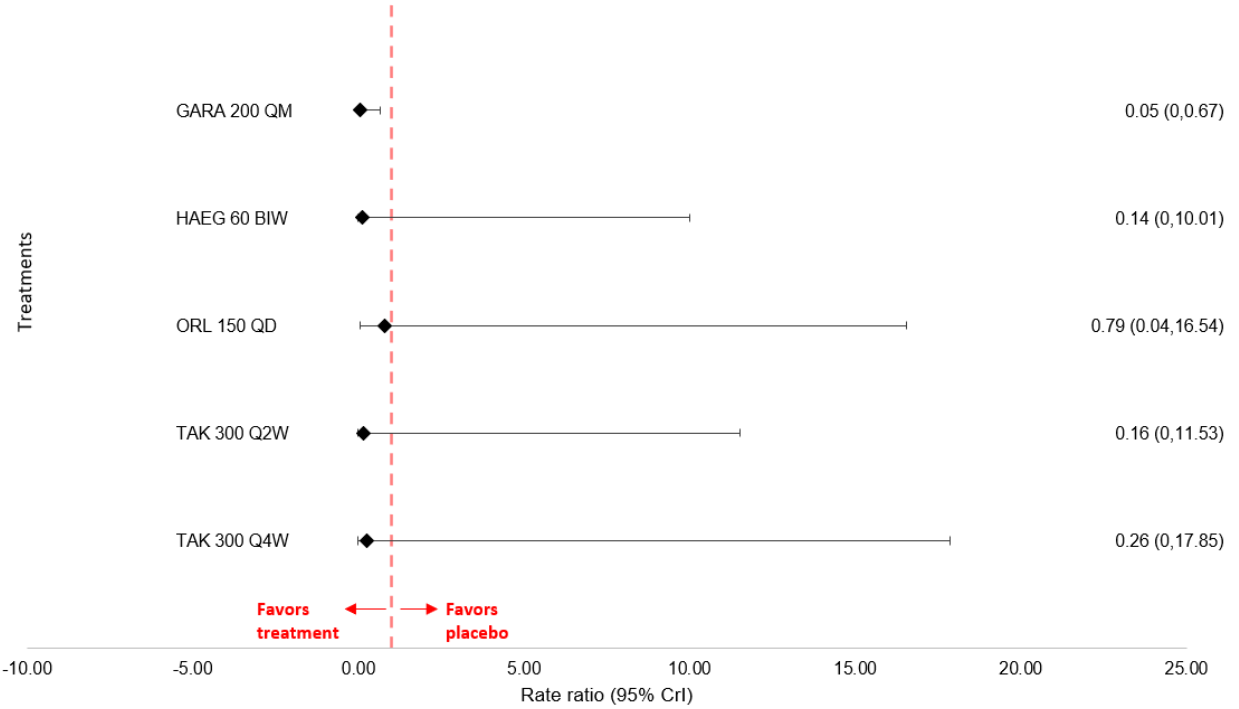
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; SUCRA = Surface Under the Cumulative Ranking curve; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 9: League table for random effects NMA of time-normalized number of moderate and/or severe HAE attacks during treatment

GARA 200 QM					
0.38 (0.00 to 40.78)	HAEG 60 BIW				
0.34 (0.00 to 41.63)	0.89 (0.00 to 392.80)	TAK 300 Q2W			
0.20 (0.00 to 21.62)	0.54 (0.00 to 222.01)	0.61 (0.01 to 42.58)	TAK 300 Q4W		
0.07 (0.00 to 2.63)	0.18 (0.00 to 28.89)	0.20 (0.00 to 36.65)	0.33 (0.00 to 57.08)	ORL 150 QD	
0.05 (0.00 to 0.67)	0.14 (0.00 to 10.01)	0.16 (0.00 to 11.53)	0.26 (0.00 to 17.85)	0.79 (0.04 to 16.54)	PBO

Note: Values are RRs (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: RR < 1 implies that column is better than row
Note: Pink squares are statistically significant
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; RR = rate ratio; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 10: Forest plot (active treatments vs. PBO) for random effects NMA of time-normalized number of moderate and/or severe HAE attacks during treatment



Abbreviations: C1INH = C1 esterase inhibitor; CrI = credible interval; Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Table 15: Random effects p-best and SUCRA scores for time-normalized number of moderate and/or severe HAE attacks during treatment

Treatment	Probability Best (%)	SUCRA (%)
PBO	0	15
GARA 200 QM	64	88
HAEG 60 BIW	16	64
TAK 300 Q2W	13	62
TAK 300 Q4W	6	48
ORL 150 QD	1	24

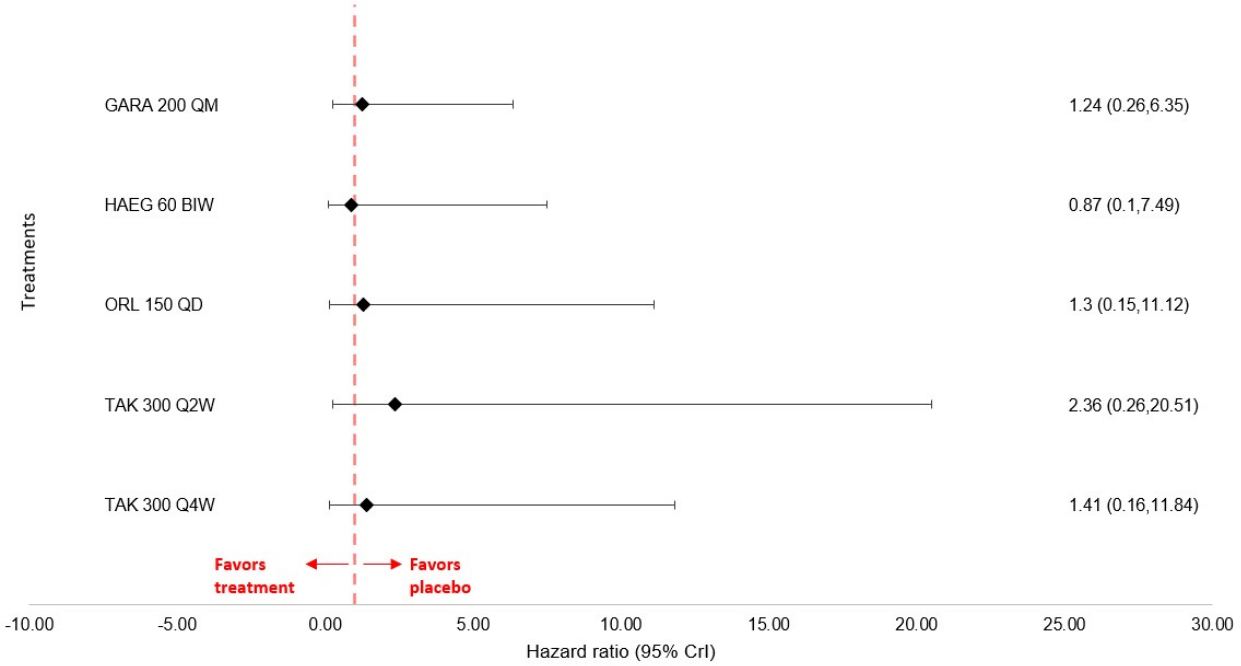
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; SUCRA = Surface Under the Cumulative Ranking curve; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 11: League table for random effects NMA of TEAEs

HAEG 60 BIW					
0.87 (0.1 to 7.49)	PBO				
0.69 (0.05 to 9.94)	0.81 (0.16 to 3.87)	GARA 200 QM			
0.67 (0.03 to 13.99)	0.77 (0.09 to 6.62)	0.96 (0.07 to 14.5)	ORL 150 QD		
0.61 (0.03 to 12.96)	0.71 (0.08 to 6.08)	0.88 (0.06 to 13.25)	0.92 (0.04 to 19.01)	TAK 300 Q4W	
0.37 (0.02 to 7.97)	0.42 (0.05 to 3.8)	0.52 (0.04 to 8.35)	0.55 (0.03 to 11.65)	0.6 (0.07 to 5.37)	TAK 300 Q2W

Note: Values are HRs (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: HR > 1 implies that column is better than row
Note: Pink squares are statistically significant
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; HR = hazard ratio; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks; TEAE = treatment-emergent adverse event

Supplementary Figure 12: Forest plot (active treatments vs. PBO) for random effects NMA of TEAEs



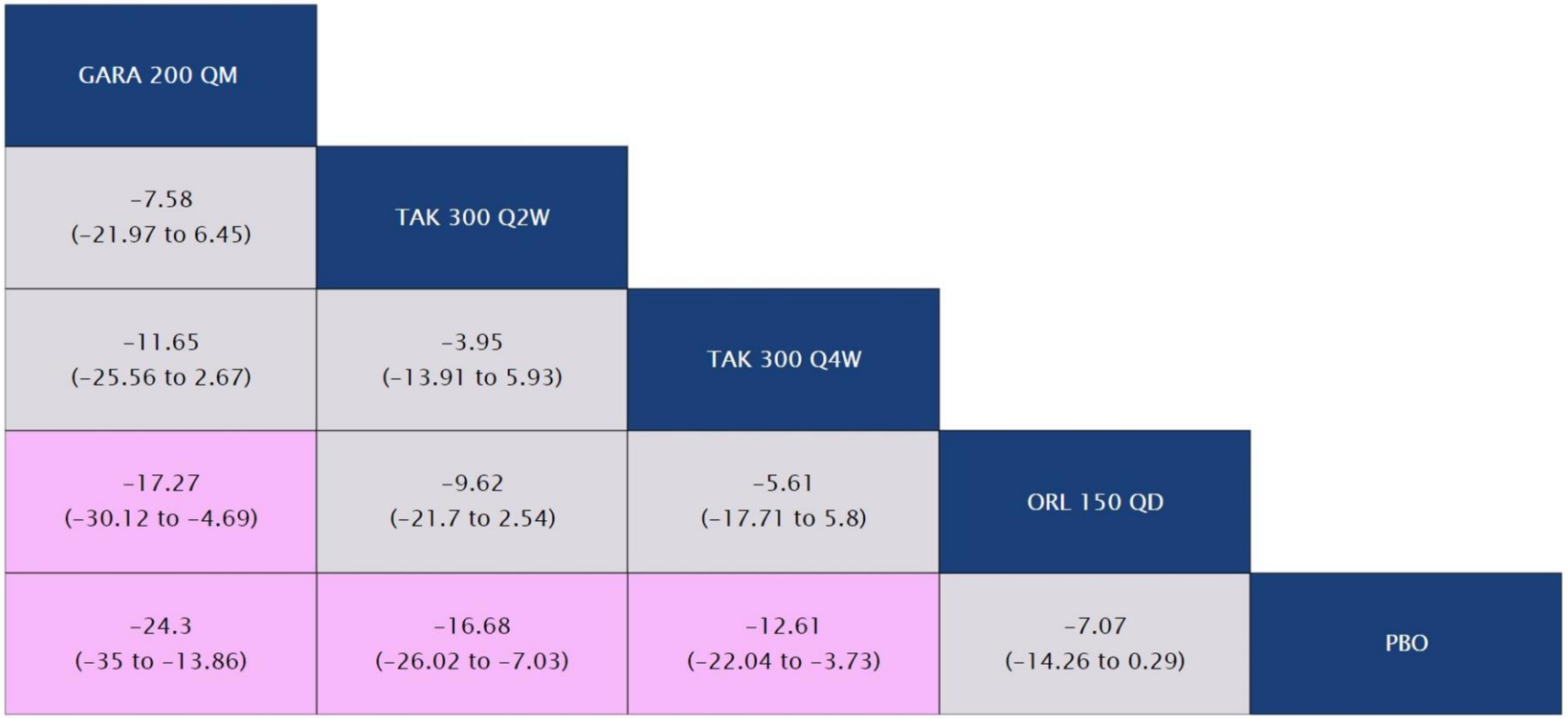
Abbreviations: C1INH = C1 esterase inhibitor; CrI = credible interval; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks; TEAE = treatment-emergent adverse event

Supplementary Table 16: Random effects p-best and SUCRA scores for TEAEs

Treatment	Probability Best (%)	SUCRA (%)
PBO	12	66
GARA 200 QM	14	50
HAEG 60 BIW	41	69
ORL 150 QD	16	48
TAK 300 Q2W	4	21
TAK 300 Q4W	13	45

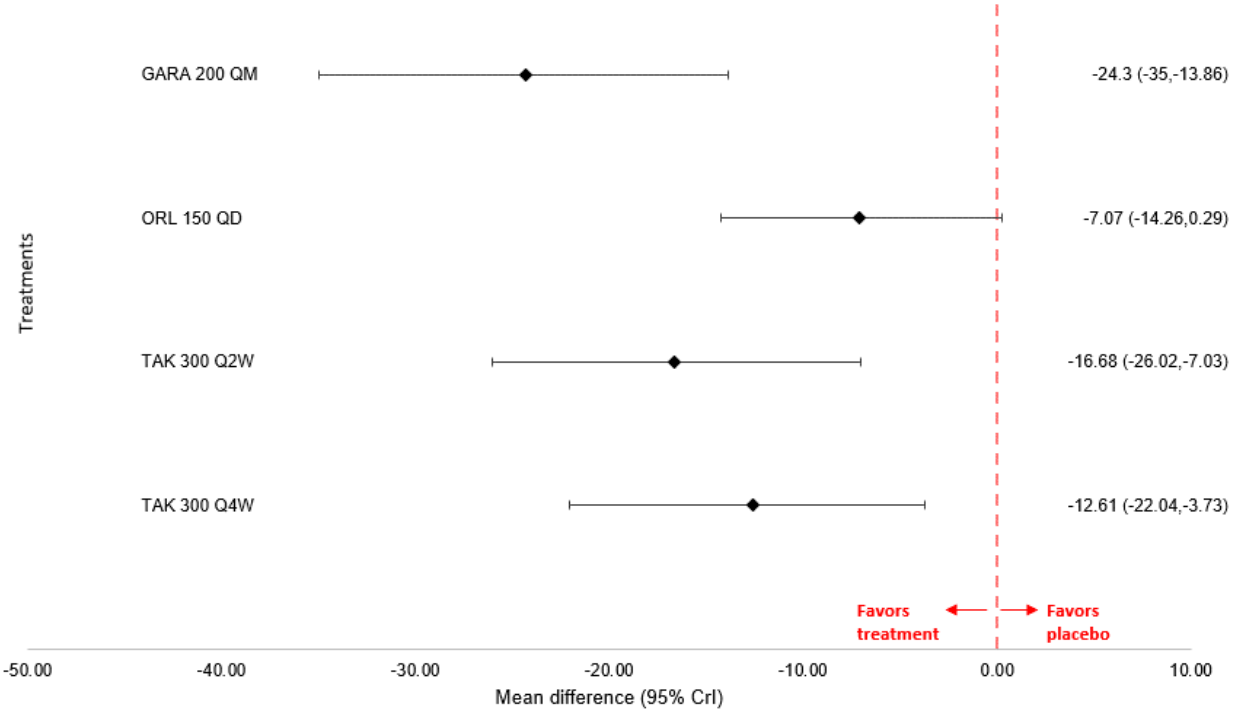
Abbreviations: C1INH = C1 esterase inhibitor; GARA 200 QM = garadacimab 200 mg once monthly; HAEG 60 BIW = subcutaneous C1INH 60 IU/kg twice weekly; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; SUCRA = Surface Under the Cumulative Ranking curve; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks; TEAE = treatment-emergent adverse event

Supplementary Figure 13: League table for random effects NMA of change from baseline in AE-QoL total score



Note: Values are Mean differences (95% credible interval) for relative effectiveness for all possible pairs of treatments in the network
Note: Mean difference < 0 implies that column is better than row
Note: Pink squares are statistically significant
Abbreviations: AE-QoL = angioedema quality of life; GARA 200 QM = garadacimab 200 mg once monthly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Figure 14: Forest plot (active treatments vs. PBO) for random effects NMA of change from baseline in AE-QoL total score



Abbreviations: AE-QoL = angioedema quality of life; CrI = credible interval; GARA 200 QM = garadacimab 200 mg once monthly; NMA = network meta-analysis; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks

Supplementary Table 17: Random effects p-best and SUCRA scores for change from baseline in AE-QoL total score

Treatment	Probability Best (%)	SUCRA (%)
PBO	0	1
GARA 200 QM	84	95
ORL 150 QD	0	30
TAK 300 Q2W	13	72
TAK 300 Q4W	3	53

Abbreviations: AE-QoL = angioedema quality of life; GARA 200 QM = garadacimab 200 mg once monthly; ORL 150 QD = berotralstat 150 mg once daily; PBO = placebo; TAK 300 Q2W = lanadelumab 300 mg once every 2 weeks; TAK 300 Q4W = lanadelumab 300 mg once every 4 weeks