**Hereditary Angioedema Attacks in Patients Receiving Long-Term Prophylaxis: A Systematic Review**

**Authors:** Hilary J. Longhurst, MD, PhD,[1] Mauro Cancian, MD,[2] Vesna Grivcheva-Panovska, MD, PhD,[3] Majed Koleilat, MD,[4] Markus Magerl, MD, PhD,[5,6] Sinisa Savic, MD, PhD,[7] Marcin Stobiecki, MD,[8] Raffi Tachdjian, MD, MPH,[9] Bridget Healy, MBChB, MPH,[10] Christopher M. Yea, PhD,[11] Paul K. Audhya, MD,[12] Laurence Bouillet, MD, PhD[13]

**Affiliations:** [1]Department of Immunology, Auckland City Hospital, Te Toka Tumai and University of Auckland, Auckland, New Zealand; [2]Department of Systems Medicine, University Hospital of Padua, Padua, Italy; [3]University Clinic of Dermatology, School of Medicine, University Saints Cyril and Methodus, Skopje, North Macedonia; [4]Deaconess Clinic, Evansville, IN, USA; [5]Angioedema Center of Reference and Excellence (ACARE) Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [6]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [7]University of Leeds, Saint James's University Hospital, Leeds, UK; [8]Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Krakow, Poland; [9]Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [10]ApotheCom, San Francisco, CA, USA; [11]KalVista Pharmaceuticals, Salisbury, UK; [12]KalVista Pharmaceuticals, Cambridge, MA, USA; [13]Grenoble Alpes University, CNRS, UMR 5525, VetAgro Sup, Grenoble INP, National Reference Center for Angioedema (CREAK), CHU Grenoble Alpes, TIMC, Grenoble, France

**Search Protocol for the Systematic Review of Attacks in Patients With Type I/II Hereditary Angioedema Receiving Long-term Prophylactic Therapy**

## Background

Hereditary angioedema (HAE) is a rare genetic disease [1,2]. People living with HAE experience painful, debilitating, and disfiguring attacks of tissue swelling, which may be life-threatening depending on the location affected [1-3]. The underlying cause is a deficiency (type I) or dysfunction (type II) of the C1 esterase inhibitor protein (C1INH), which in turn leads to uncontrolled activation of the kallikrein kinin system and release of bradykinin, triggering fluid extravasation and edema [4].

European Medicines Agency– and US Food and Drug Administration (FDA)–approved drugs for long-term prophylaxis (LTP) in people living with HAE are plasma-derived C1 inhibitor proteins (Cinryze® and Haegarda® [sc-Berinert®]), the plasma kallikrein inhibitors lanadelumab (Takhzyro®, a monoclonal antibody) and berotralstat (Orladeyo®) [1, 2]. HAE clinical guidelines indicate that attenuated androgens (eg, danazol, stanozolol) may also be used as a second-line treatment where first-line LTP options are not available [1,2]. Antifibrinolytic therapy with tranexamic acid (Cyklokapron® and Lysteda®) or epsilon aminocaproic acid (Amicar®) are also used as a second-line treatment for patients in whom the use of attenuated androgens is contraindicated, although they are not recommended by most international guidelines [1] and approval of these agents varies internationally. A study evaluating garadacimab, an investigational monoclonal antibody against factor XII, recently reported positive phase 3 trial results [5], although garadacimab had yet to receive approval in any country.

People with HAE receiving LTP may continue to experience HAE attacks [6]. These attacks have been named ‘breakthrough attacks’ [7], although there is currently no scientific rationale to suggest that attacks which occur when receiving LTP are mechanistically different from attacks that occur in the absence of LTP. HAE clinical guidelines therefore recommend that all people living with HAE have immediate access to ≥2 doses of an effective on-demand treatment at all times, including

patients receiving LTP [1, 2]. This systematic literature review will assess attacks in people with HAE receiving LTP and thereby provide insight into the continued need for on-demand therapies.

## Objectives

### Primary objective

- To determine the proportion of people with HAE-C1INH receiving LTP who continue to experience attacks

### Secondary objectives

- To characterize the nature of attacks in patients with HAE-C1INH receiving LTP (eg, attack severity, duration, and location in the body)
- To describe the characteristics of patients with HAE-C1INH who continue to experience attacks while receiving LTP
- To report on the use of on-demand therapies to treat attacks occurring in patients with HAE-C1INH receiving LTP, including the need for a second on-demand dose

### Search strategy

- **Search database:** PubMed
- **Search query:**

  ("Hereditary angioedema" OR “hereditary angioedemas” OR “hereditary angiooedema” OR "hereditary angio-edema" OR "hereditary angio-oedema" OR “hereditary angioneurotic edema” OR “hereditary angioneurotic oedema” OR “hereditary angio-neurotic edema” OR “hereditary angio-neurotic oedema”)

  AND

  (“C1 esterase inhibitor” OR “C1 inhibitor” OR “C1INH” OR “C1-INH” OR “Cinryze” OR “Cetor” OR “Haegarda” OR “Lanadelumab” OR “Monoclonal antibodies” OR “Monoclonal

antibody" OR "Berotralstat" OR "Kallikrein" OR "Biologic" OR "Biologics" OR "Androgen" OR "Androgens" OR "Anabolic steroid" OR "Anabolic steroids" OR "Danazol" OR "Stanozolol" OR "Oxandrolone" OR "Methyltestosterone" OR "Aminocaproic acid" OR "6-aminohexanoic acid" OR "Amicar" OR "Tranexamic acid" OR "Treatment" OR "Treatments" OR "Therapy" OR "Therapies" OR "Therapeutic" OR "Therapeutics" OR "Prophylaxis" OR "Prophylactic" OR "Prevention" OR "Prevent" OR "Management" OR "Breakthrough")

- **PubMed search parameters:** No PubMed search parameters/filters are to be applied during the search, other than limiting the search to articles in English published in the timeframe indicated below, to allow all search results to be collected and then manually reviewed
- **Timeframe:** Past 20 years (search results published on or after January 1, 2002, to present)
- **Original search date:** May 17, 2022
- **Updated search:** To ensure that the search remains up to date, the search will be repeated in PubMed with the same search query
- **Updated search date:** May 15, 2023
    - Timeframe for the updated search is May 17,2022 to present

**LTP agents to be included in the SLR**

- Studies should be those that report HAE attacks in patients with HAE-C1INH (i.e., type I/II HAE) receiving LTP
- In the original SLR protocol, LTP agents were restricted to those that are FDA-approved for HAE and those that are/were used for HAE prophylaxis (as indicated in HAE clinical guidelines) but are not necessarily indicated for this in the product labels. Specifically, these treatments would be C1 esterase inhibitor protein (Cinryze® and Haegarda®), lanadelumab (Takhzyro®), berotralstat (Orladeyo®), androgen steroids (danazol, stanozolol, oxandrolone, and methyltestosterone), and antifibrinolytics (aminocaproic acid and tranexamic acid)

- In this protocol amendment (dated May 15, 2023), LTP agents that have reported phase 2/3 clinical trial findings (ie, garadacimab, donidalorsen) will also be included in the systematic search[a]
    - Investigational LTP agents that only have phase 2 findings will be discussed in a subsection of the Results on 'LTP agents in early phase clinical development'

**Content sources**

- Both the original search and updated search are being conducted in **PubMed** to identify articles published in peer-reviewed journals in the past 21 years (limited to articles published in English language only)
- **Congresses** will NOT be searched because abstracts and presentations are not peer reviewed, they typically do not report full data, and presentations are often not available
- **Press releases** will NOT be searched because they are not peer reviewed and only report small amounts of high-level data
- Reference lists of key articles found in the PubMed search will be checked for additional relevant articles
- Relevant articles that are not found in the PubMed search may be manually added to the final list of articles
- **Manual review:** medical writer will review each search result for relevance as follows:
    - 1) All articles identified in the search results will be reviewed at the title/abstract level
    - 2) If deemed suitable by review of the title/abstract, the full text will then be reviewed to assess for inclusion in the final set of articles
        - All excluded articles will be documented with reason for exclusion

- **The following search results will be excluded:**
    - Review, opinion, perspective, and editorial articles

        - Review articles will be flagged to allow for later retrieval. They can be checked to identify any relevant articles not found in the PubMed search
    - Guidelines (eg, clinical guidelines)
    - SLR and meta-analysis articles (to avoid capturing the same data twice)
        - SLR and meta-analysis articles on HAE attacks in patients receiving LTP will be flagged to allow for later retrieval
    - Case reports
    - Preclinical, animal, in vitro, in silico, or otherwise non-human studies
    - News and views articles, news articles, and press releases
    - Books
    - Entries where the full article is not available
    - Entries that are not available in English
    - Articles that have been retracted or are otherwise not appropriate to include
    - Duplicate articles (each article should be present only once in the list of search results)
    - Studies that do NOT report on type I/II HAE, including studies that report on HAE with normal C1 esterase inhibitor protein (formerly called type 3) and studies where it is not clear whether they are reporting on type I/II HAE
    - Studies that report patients taking only on-demand therapy or only short-term prophylaxis therapy (ie, prophylaxis taken prior to a medical, surgical, or dental procedure that may trigger an attack)
    - Studies that do not report on an efficacy outcome considered relevant for the SLR. Examples of efficacy outcomes are listed in Appendix 1

- **Updated Search**
    - In the original search [May 17, 2022], studies must have reported on attacks in patients with type I/II HAE receiving one of the following LTP agents: C1INH (Cinryze or Haegarda), lanadelumab (Takhzyro), berotralstat (Orladeyo), androgens

(danazol, stanozolol, oxandrolone, or methyltestosterone), aminocaproic acid, or tranexamic acid

- In the updated search [May 15, 2023], studies must have reported on attacks in patients with type I/II HAE receiving one of the LTP agents listed above for the original search **OR** an investigational LTP agent (ie, currently in clinical development) which has published phase 2/3 clinical trial results available (including garadacimab and donidalorsen)[a]

**Final set of included articles**

- Reference lists of the final set of articles (ie, those remaining after excluding search result entries per the above defined criteria) will be checked for additional relevant articles to manually add to the final list
    - Finally, the list will be checked to ensure that each article is present only once
- These criteria should result in a list of articles reporting HAE attacks in studies of patients with type I/II HAE receiving LTP; the LTP agents should be approved or commonly used for preventing HAE attacks (based on HAE clinical guidelines) or investigational LTP agents which have published phase 2/3 efficacy results
- A PRISMA diagram will be used to report the number of PubMed search results from the original and updated searches, number of entries that were excluded/included during each search, number of entries that were manually added, and number of entries in the final list
    - Investigational LTP agents that only have phase 2 findings will be included in the PRISMA flow diagram of included studies, but as only limited data will be available, we will discuss these agents in a subsection of the Results on 'LTP agents in early phase clinical development'

**References for the Study Protocol**


1. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. J Allergy Clin Immunol Pract 2021;9(1):132-50.e3. doi:10.1016/j.jaip.2020.08.046

2. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. Allergy 2022;77(7):1961-90. doi:10.1111/all.15214

3. Bork K, Anderson JT, Caballero T, Craig T, Johnston DT, Li HH, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy Asthma Clin Immunol 2021;17(1):40. doi:10.1186/s13223-021-00537-2

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5. Craig TJ, Reshef A, Li HH, Jacobs JS, Bernstein JA, Farkas H, 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. Lancet 2023;401(10382):1079-90. doi:10.1016/S0140-6736(23)00350-1

6. Longhurst H. Optimum use of acute treatments for hereditary angioedema: evidence-based expert consensus. Front Med (Lausanne) 2017;4:245. doi:10.3389/fmed.2017.00245

7. Aberer W, Maurer M, Bouillet L, Zanichelli A, Caballero T, Longhurst HJ, et al. Breakthrough attacks in patients with hereditary angioedema receiving long-term prophylaxis are responsive to icatibant: findings from the Icatibant Outcome Survey. Allergy Asthma Clin Immunol 2017;13:31. doi:10.1186/s13223-017-0203-z

**Appendix 1**

List of example efficacy outcomes considered relevant for inclusion in the SLR:

- Proportion of patients who are attack free (primary outcome of interest)
- Rate of HAE attacks
- Proportion of patients with attacks
- Number or rate of attacks requiring on-demand therapy
- Number or rate of attacks by body location
- Percentage or responders (ie, percentage of patients who experienced a reduction in attacks beyond a specific threshold)
- Number or rate of attacks by severity
- Proportion of patients with attacks by location
- Proportion of patients with attacks by severity
- Duration of attacks
- Attack severity score/symptom severity score
- Number of days with angioedema symptoms
- Duration of attack-free period
- On-demand/rescue medication use
- Proportion of patients with attacks requiring on-demand therapy or additional medical care

**Table S1. Primary studies included in the systematic review**

| Study identifier | First author, year | Study design | LTP agent | Dose | Comparator | No. of patients | Study population | Duration of treatment | Primary outcome | Risk of bias/quality |
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| **RCTs and open-label extension studies** | | | | | | | | | | |
| **pdC1INH replacement** | | | | | | | | | | |
| NCT02052141 | Aygören-Pürsün, 2019 [23] | Phase 3<br>Crossover<br>Single-blind<br>Multicenter | Cinryze (IV) | 500 U<br>1000 U | NA | 12 | Children aged ≥6 to <12 years | 2 × 12-week crossover periods | Monthly normalized number of attacks in each 12-week treatment period | High risk |
| NCT01005888 (LEVP2005-1 Part B) | Lumry, 2013 [21]<br>Zuraw, 2010 [42] | Phase 3<br>Crossover<br>Double-blind<br>Multicenter | Cinryze (IV) | 1000 U | Placebo | 24 | Children aged ≥6 years and adults | 2 × 12-week crossover periods | Normalized number of attacks in each 12-week treatment period | Low risk |
| NCT00462709 (LEVP2006-4 CHANGE-3) | Zuraw, 2012 [14]<br>Lumry, 2013 [21]<br>Zuraw, 2010 [42]<br>Baker, 2013 [22] | Phase 3<br>Open-label extension<br>Multicenter | Cinryze (IV) | 1000 U | NA | 146 | Children aged ≥1 year and adults | Median: 248 days (up to 2.6 years) | Number of attacks during the treatment period | NA |
| NCT01576523 | Zuraw, 2015 [15] | Phase 2<br>Open-label<br>Crossover<br>Multicenter | Berinert (SC) | 1500 IU<br>3000 IU<br>6000 IU | NA | 18 | Adults aged ≥18 years | 2 × 4-week treatment periods | Mean trough C1INH activity at week 4[a] | NA |
| NCT01912456 (COMPACT) | Longhurst, 2017 [9]<br>Craig, 2019 [44]<br>Li, 2019 [41] | Phase 3<br>Crossover<br>Double-blind<br>Multicenter | Berinert (SC) | 40 IU/kg<br>60 IU/kg | Placebo | 90 | Adolescents aged ≥12 years and adults | 2 × 16-week crossover periods | Time-normalized number of attacks in each 16-week treatment period | Moderate risk |
| NCT02316353 (COMPACT-OLE) | Craig, 2019 [43]<br>Craig, 2022 [13]<br>Bernstein, 2020 [19]<br>Levy, 2020 [18]<br>Levy, 2020 [56] | Phase 3<br>Open-label extension<br>Parallel<br>Multicenter | Berinert (SC) | 40 IU/kg[b]<br>60 IU/kg[b] | NA | 126 | Children aged ≥6 years and adults | ≥52 weeks to 140 weeks[c] | Long-term safety[d] | NA |
| Japanese study | Fukuda, 2023 [20] | Phase 3<br>Open-label<br>Single-arm<br>Multicenter | Berinert (SC) | 60 IU/kg | Baseline (3-month period before screening) or run-in (up to 8 weeks) | 9 | Adolescents aged ≥12 years and adults | 16 weeks | Time-normalized number of attacks/month during the treatment period; C1INH activity at week 16[e] | NA |

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| **Lanadelumab** | | | | | | | | | | |
| NCT02093923 | Banerji, 2017 [50] | Phase 1b<br>Parallel<br>Double-blind<br>Multicenter | Lanadelumab | 30 mg<br>100 mg<br>300 mg<br>400 mg | Placebo | 37 | Adults aged ≥18 years | 6 weeks[f] | Number of attacks per week from day 8 to day 50 | Moderate risk |
| NCT02586805 (HELP) | Banerji, 2018 [8]<br>Johnston, 2021 [57]<br>Riedl, 2020 [16]<br>Craig, 2022 [58] | Phase 3<br>Parallel<br>Double-blind<br>Multicenter | Lanadelumab | 150 mg<br>300 mg (Q2W)<br>300 mg (Q4W) | Placebo | 125 | Adolescents aged ≥12 years and adults | 26 weeks | Number of attacks in the 26-week treatment period | Low risk |
| NCT02741596 (HELP-OLE) | Banerji, 2022 [24]<br>Craig, 2022 [58] | Phase 3<br>Open-label extension<br>Multicenter | Lanadelumab | 300 mg[g] | NA | 212 | Adolescents aged ≥12 years and adults | Mean (SD): 29.6 (8.2) months | Long-term safety; number of investigator-confirmed HAE attacks per month during the treatment period[h] | NA |
| **Berotralstat** | | | | | | | | | | |
| NCT02870972 (ApeX-1) | Aygören-Pürsün, 2018 [33] | Phase 2<br>Parallel<br>Double-blind<br>Multicenter | Berotralstat | 62.5 mg<br>125 mg<br>250 mg<br>350 mg | Placebo | 77[i] | Adults aged 18 to 70 years | 28 days | Number of confirmed attacks from day 8 to day 28 (the effective dosing period) | Low risk |
| NCT03485911 (ApeX-2) | Zuraw, 2021 [10]<br>Wedner, 2021 [35] | Phase 3<br>Parallel<br>Double-blind<br>Multicenter | Berotralstat | 110 mg<br>150 mg | Placebo[j] | 121[k] | Adolescents aged ≥12 years and adults[l] | 48 weeks | Rate of confirmed attacks during the 24-week treatment period (part 1); long-term safety (part 2)[m] | Low risk |
| NCT03873116 (ApeX-J) | Ohsawa, 2021 [59] | Phase 3<br>Parallel<br>Double-blind<br>Multicenter | Berotralstat | 110 mg<br>150 mg | Placebo[j] | 19 | Adolescents aged ≥12 years and adults | 52 weeks | Rate of confirmed attacks during the 24-week placebo-controlled treatment period | Low risk |
| NCT03472040 (ApeX-S) | Farkas, 2021 [34] | Phase 3<br>Open-label extension<br>Parallel<br>Multicenter | Berotralstat | 150 mg<br>110 mg[n] | NA | 227 | Adolescents aged ≥12 years and adults[o] | 48 weeks | Long-term safety and tolerability[p] | NA |

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| **Investigational LTP agents** | | | | | | | | | | |
| NCT03712228 | Craig, 2022 [60] | Phase 2<br>Parallel<br>Double-blind<br>Multicenter | Garadacimab | 75 mg[q]<br>200 mg[q]<br>600 mg[q] | Placebo | 32 | Adults aged 18 to 65 years | 12-week SC administration period[r] | Time-normalized number of attacks per month during the SC treatment period | Low risk |
| NCT04656418 (VANGUARD) | Craig, 2023 [17] | Phase 3<br>Parallel<br>Double-blind<br>Multicenter | Garadacimab | 200 mg[s] | Placebo | 64 | Adolescents aged ≥12 years and adults | 6 months | Time-normalized number of attacks (attacks/month) during the 182-day treatment period | Low risk |
| NCT04030598 (ISI 721744-CS2) | Fijen, 2022 [51] | Phase 2<br>Parallel<br>Double-blind<br>Multicenter | Donidalorsen | 80 mg | Placebo | 20 | Adults aged ≥18 years | 16 weeks | Time-normalized number of attacks per month from baseline (week1) to week 17 | Low risk |
| NCT02584959 (SAHARA) | Lumry, 2019 [61] | Phase 3,<br>Partial crossover<br>Double-blind<br>Multicenter | SHP616 (SC pdC1INH with hyaluronidase) | 2000 IU | Placebo | 75 | Adolescents aged ≥12 years and adults[t] | 2 × 14-week crossover periods or 28 weeks of active treatment | Monthly normalized number of attacks during the treatment period | Low risk |
| NCT02247739 | Riedl, 2017 [62] | Phase 2<br>Crossover<br>Double-blind<br>Multicenter | Ruconest (recombinant C1INH) | 50 IU/kg[u] | Placebo | 32 | Adolescents aged ≥13 years and adults | 3 × 4-week crossover periods | Number of attacks in each 4-week treatment period | Low risk |
| Pilot study | Reshef, 2013 [63] | Phase 2<br>Open-label<br>Single-arm<br>Multicenter | Ruconest (recombinant C1INH) | 50 IU/kg | NA | 25 | Adults aged 18 to 65 years[v] | 8 weeks | Number of attacks during the treatment period | NA |
| **Real-world evidence and other non RCT/OLE studies** | | | | | | | | | | |
| NCT01034969 (Icatibant Outcome Survey) | Aberer, 2017 [36] | Prospective registry | pdC1INH (IV)<br>Androgens<br>TA | NR | Patients not receiving LTP | 448 | Patients who have taken ≥1 dose of Firazyr[v] | Mean (SD): 3.5 (1.8) years per patient on LTP | NR | 7 stars |
| Johannes-Gutenberg University, Germany. Semmelweis University, Hungary | Füst, 2011 [39] | Prospective cohort | Danazol | Mean:<br>136 mg (Germany)<br>128 mg (Hungary) | NR | 84 | Patients from Germany and Hungary[v] | ≥6 years | NR | 7 stars |

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| Semmelweis University, Hungary (Grant: OTKA-NKTH 100886) | Farkas, 2013 [64] | Prospective cohort | Danazol<br>TA<br>Aminocaproic acid | Mean: 86 mg/day (danazol) 1262 mg/day (TA) | NA | 48 | Children aged <18 years (Hungary) | Mean: 6 years[w] | NA | 6 stars |
| Angioedema Center of Reference and Excellence, Charité, Germany | Buttgereit, 2021 [65] | Prospective cohort | Lanadelumab | NR | NR | 30 | Adults aged 19 to 78 years[v] (Germany) | Median (range): 29.9 (3.3-65.3) weeks | NR | 6 stars |
| Hospitals in Denmark | Rasmussen, 2016 [37] | Prospective cohort | Cinryze (IV) | 1000 U | Baseline (prior to receiving LTP with C1INH) | 6 | Adults from Denmark[v] | Median (range): 8.5 (4-15) months | NR | 6 stars |
| Hospitals in Switzerland | Steiner, 2016 [30] | Retrospective cohort | Danazol<br>TA | NR | NR | 104 | Children and adults aged 5 to 80 years[v] (Switzerland) | 1 year | NR | 5 stars |
| IAHAE-registered patients | Zanichelli, 2011 [49] | Prospective cohort | Danazol<br>Stanozolol<br>TA | Danazol: 50-200 mg<br>Stanozolol: 2-4 mg<br>TA:1.5-3 g | NR | 103 | Children and adults aged 5 to 93 years[v] (Italy) | NR | NR | 5 stars |
| University Hospital of Ulm, Germany | Hahn, 2020 [46] | Prospective cohort | Lanadelumab | 300 mg | Prior to enrolment (when receiving on-demand therapy only) | 12 | Patients aged 16 to 73 years[v] (Germany) | ≥6 months | NR | 4 stars |
| Hospitals in Australia | Katelaris, 2023 [48] | Prospective cohort | Danazol[x]<br>TA<br>C1INH (IV)[x]<br>C1INH (SC)[x]<br>Lanadelumab[x]<br>Berotralstat[y] | NR | Patients only receiving on-demand therapy | 50 | Adolescents aged ≥12 years and adults (Australia) | Mean: 9.1 months | NR | 4 stars |
| University Clinics in Ulm or Munich, Germany | Greve, 2016 [66] | Prospective cohort | Cinryze | 1000 U | Prior to enrollment (when receiving on-demand therapy only) | 7 | Adults aged 26 to 72 years[v] (Germany) | 12 months | NR | 3 stars |

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| US-HAEA | Zuraw, 2016 [27] | Patient survey | Attenuated androgens | Variable | Patients who had never used androgens and patients who had previously used but discontinued androgens | 650 | Patients from the United States[v] | NA | NR | 3 stars |
| United Kingdom audit | Dorr, 2023 [45] | Retrospective chart review | Lanadelumab | NR | Baseline (prior to commencing lanadelumab) | 62 | Patients from the United Kingdom[v] | Up to 12 months | NR | 3 stars |
| United Kingdom audit | Ahuja, 2023 [47] | Patient survey | Berotralstat | 150 mg | Baseline (3-month period prior to commencing berotralstat) | 54 | Patients from the United Kingdom[v] | 6 months | NA | 2 stars |
| Peking Union Medical College Hospital, China (S-K661) | Liu, 2020 [28] Xu,2022 [67] | Retrospective cohort/registry | Danazol[z] TA | Danazol: <200-600 mg[z] TA: 0.9-3 g | NA | 107[z] | Children and adults aged ≥11 years[v] (China) | NR | NR | 6 stars |
| Johannes-Gutenberg University, Germany | Bork, 2003 [30] | Retrospective chart review | Danazol | 50-200 mg | NR | 123 | Children and adults aged ≥3 years[v] (Germany) | Mean: 7.4 years | NR | 6 stars |
| University of Mainz, Germany University of Odense, Denmark | Bork, 2008 [38] | Retrospective chart review | Danazol | 100-600 mg | Attack rate in the 3-year period prior to commencing danazol | 118 | Patients aged 15 to 74 years from Germany and Denmark[v] | Mean: 11.0 years | Mean number of attacks per year during the treatment period | 6 stars |
| Hospitals in South Korea | Jung, 2018 [68] | Retrospective chart review | Danazol TA | Danazol: mean 231.5 mg TA: mean 666.7 mg | Prior to commencing LTP | 65 | Patients from Korea[v] | Mean (SD): 4.1 (4.6) years | NR | 6 stars |

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| Hospitals in Poland | Piotrowicz-Wójcik, 2021[69] | Patient survey | Danazol<br>TA | NR | Patients receiving on-demand treatment only | 138 | Adults aged ≥18 years from Poland | NR | NR | 6 stars |
| National Reference Centre for Angioedema (CREAK) | Wintenberger, 2014 [31] | Retrospective chart review | TA | Median:<br>3 g | Baseline (6 months prior to commencing TA) | 12 | Patients aged ≥16 years (France) | Median:<br>34 months | NR | 6 stars |
| Hospital Universitario La Paz, Spain | Gomez-Traseira, 2015[70] | Retrospective chart review | Danazol<br>Stanozolol<br>TA<br>Berinert (IV) | Mean weekly dose: 6.7 mg (stanozolol)<br>561.1 mg (danazol)<br>6666.7 mg (TA)<br>3250 U (Berinert) | NA | 112 | Children and adults aged 4 to 75 years[v] (Spain) | NR | NR | 5 stars |
| Single-center (Location not stated) | Abuzakouk, 2022 [26] | Retrospective chart review | Lanadelumab | 300 mg | Baseline (prior to commencing lanadelumab) | 9 | Adults aged 21 to 55 years[v] switching from another LTP agent | Median:<br>36 weeks | NR | 6 stars |
| Academic hospitals, Canada | Iaboni, 2021[25] | Retrospective chart review | Lanadelumab | 300 mg | Baseline (1 year prior to commencing lanadeluamb) | 12 | Adults aged 24 to 74 years[v] (Canada) | 12 months | NA | 5 stars |
| Czech national registry | Hakl, 2022 [40] | Retrospective chart review | Danazol<br>TA<br>C1INH (SC or IV pdC1INH, or IV recombinant C1INH) | NR | NA | 66 | Children and adults aged 5 to 74 years[v] with a laryngeal attack (Czech) | NR | NR | 4 stars |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HUCFF-UFRJ, Brazil | Lima, 2020 [71] | Retrospective chart review | Danazol<br>Oxandrolone<br>Aminocaproic acid<br>TA<br>C1INH (exact product and administration route not specified) | Variable | NA | 10 | Patients aged 16 to 70 years[v] undergoing dental surgery (Brazil) | 7 days post procedure | NR | 3 stars |
| Latvian Council of Science (lzp-2020/1-0269) | Kanepa, 2023 [72] | Physician survey | Danazol<br>TA | NR | NA | 10 | Adults aged 32 to 63[v] (Latvia) | NR | NR | 3 stars |

*ATU,* authorization for temporary use; *C1INH,* C1 inhibitor; *HAE,* hereditary angioedema; *HUCFF-UFRJ,* Hospital Universitario Clementino Fraga Filho of the Federal University of Rio de Janeiro; *IAHAE,* Italian Association of Patients with Hereditary Angioedema; *IV,* intravenous; *LTP,* long-term prophylaxis; *NA,* not applicable; *NR,* not reported; *Q2W,* every 2 weeks; *Q4W,* every 4 weeks; *SC,* subcutaneous; *TA,* tranexamic acid; *TEAE,* treatment-emergent adverse events; *US-HAE,* United States Hereditary Angioedema Association.

[a]The primary endpoint of mean trough C1INH functional activity were model-derived rather than observed trough levels. [b]Eligible patients were randomly assigned to receive sc-Berniert with a dose of either 40 or 60 IU/kg twice weekly for 52 weeks. However, during the first 24 weeks of treatment, patients experiencing ≥12 HAE attack per 4-week evaluation period were eligible for incremental dose increases of 20 IU/kg (up to a maximum of 80 IU/kg) at the discretion of the investigator. In the second treatment period of 28 weeks, patients experiencing ≥3 HAE attacks per 8-week evaluation period were eligible for dose increases to optimize treatment response. [c]Patients in the United States had the option to continue treatment for up to 140 weeks. [d]The primary prespecified safety endpoints were person-time incidence rates of related serious adverse events, adverse events leading to premature discontinuation, adverse events of special interest (thromboembolic events and anaphylaxis), HAE attacks resulting in hospitalization, severe injection site reactions (grade by the investigator), and the development of neutralizing anti-C1INH antibodies. [e]The study reported 2 primary endpoints. [f]Patients received 2 subcutaneous injections of study drug, given 14 days apart. The primary efficacy analysis included the number of attacks during the 6-week interval from days 8 to 50. [g]In rollover patients, a single dose of lanadelumab 300 mg was received at study entry until the patient experienced their first attack, following which the patient received lanadelumab 300 mg Q2W. Nonrollover patients received lanadelumab 300 mg Q2W from day 0. [h]The efficacy endpoint was a secondary outcome. Efficacy analyses for rollover patients were based on occurrence of attacks during the regular Q2W dosing stage and the first HAE attack during the dose-and-wait period was not counted. [i]Of the 77 patients who underwent randomization, 2 patients did not receive any study treatment. [j]In the APeX-2 and APeX-J studies, patients were randomized to berotralstat 150 mg, berotralstat 110 mg, or placebo for 24 weeks in part 1. Patients receiving placebo in part 1 were rerandomized to berotralstat 150 or 110 mg in part 2. [k]One hundred twenty-one patients were randomized and 120 were treated in part 1, and 108 patients completed dosing in part 1 and received ≥1 dose of berotralstat in part 2. [l]Patients in the United States and Canada were required to be ≥12 years of age and patients in Europe were required to be ≥18 years of age. [m]The long-term safety primary endpoints included the number and proportion of patients with TEAEs, serious TEAEs, grade 3 or 4 TEAEs or laboratory abnormalities, and rash. [n]The study was initially designed to evaluate berotralstat 150 mg over 48 weeks of treatment, but the protocol was amended to include the berotralstat 110-mg dose. [o]Patients were eligible in all participating countries if aged ≥18 years and if aged ≥12 years in certain countries. [p]Safety endpoints included the proportion of patients with TEAEs, grade 3 or 4 TEAEs or treatment-emergent laboratory abnormalities, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs consistent with drug rash. [q]Initial intravenous loading doses of placebo 40, 100, and 300 mg were administered on day 1, followed by subcutaneous treatment with placebo or 75, 200, and 600 mg of garadacimab, respectively, on day 6 and every 4 weeks thereafter for 12 weeks. [r]The primary endpoint was assessed during the 12-week SC administration period from days 6 to 63. [s]Following an initial loading dose of 400 mg of garadacimab. [t]Patients in Germany and Israel were required to be ≥18 years of age to be eligible. [u]Ruconest dosing was 50 IU/kg for patients weighing <84 kg or 4200 IU for patients weighing ≥84 kg. [v]An age range for eligibility was not stated. [w]Pediatric patients were followed up from diagnosis until 18 years of age. [x]Danazol was difficult to access during the study owing to local supply discontinuation, IV C1INH use for LTP was being used off label in Australia and was only available for patients who had ≥8 documented attacks per month, SC C1INH became available in Australia during the study and was only available for patients who had ≥8 documented attacks per month, and lanadelumab was only available through compassionate access. [y]Berotralstat was received as part of a clinical trial and was not approved for use in Australia at the time the study was conducted. [z]Liu et al reported treatment patterns in 107 patients with HAE in China and Xu et al reported on a subset of 74 patients receiving LTP with danazol.

**Table S2. Attack severity in patients who received LTP in phase 3 non-placebo-controlled trials and real-world observational studies**

| First author, year of publication | Duration of treatment | No. of patients | Assessment of attack severity | LTP agent and dose | Attack severity, mean (SD) or n (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Baseline | LTP | *P* value |
| Aygören-Pürsün, 2019 [23] | 2 × 12-weeks | 12 | Attack severity score, mean (SD)[a] | Cinryze 500 U every 3-4 days | 7.2 (6.0) | 2.0 (2.9)[b] | NR |
| Rasmussen, 2016 [37] | 4-15 months | 6 | Attack severity score, mean (SD)[a] | Cinryze 1000 U every 3-4 days | 2.1 | 2.3 | NR |
| Fukuda, 2023 [20] | 16 weeks | 9 | Time-normalized relative reduction in moderate-to-severe attacks | Berinert 60 IU/kg twice weekly | NR | 88.8% relative reduction | 0.008 |
| Dorr, 2023 [45] | Up to 12 months | 62 | Number of severe attacks per month, mean (SD) | Lanadelumab 300 mg Q2W | 7.2 (7.2) | 0.4 (1.4) 6 months | NR |
| | | | | | | 0.3 (0.7) 12 months | |
| Hahn, 2020 [46] | ≥6 months | 12 | Reduction in the number of mild, moderate, and severe attacks per month | Lanadelumab 300 mg Q2W | NR[c] | Mild | 0.008 |
| | | | | | | Moderate | <0.0001 |
| | | | | | | Severe | 0.0001 |
| Banerji, 2022 [24] | 29.6 months (mean) | 212 | Number of moderate or severe attacks per 4 weeks, mean | Lanadelumab 300 mg Q2W[d] | 2.0 | 0.2 | NR |
| Ahuja, 2023 [47] | 6 months | 54 | Attack severity score, mean (SD)[e] | Berotralstat 150 mg QD | 3.5 (0.8) | 2.3 (1.2) | <0.0001 |
| Zuraw 2016 [28] | NA | 334[f] | Attack severity score, mean (SD)[e] | Attenuated androgens | 4.3 (0.1) | 2.5 (0.1) | <0.0001 |
| Aberer, 2017 [36] | 3.5 years (mean) | 448 | Proportion of attacks rated as severe/very severe, % | C1INH | 53 | 46 | 0.193 |
| | | | | Androgens | 53 | 69 | 0.043 |
| | | | | TA | 53 | 53 | 0.989 |
| Katelaris, 2023 [48] | 9.1 months (mean) | 49 | Proportion of attacks rated as severe or significant, % | SC C1INH | 22 | 35 | NR |
| | | | | IV C1INH | 22 | 23 | NR |
| | | | | Danazol | 22 | 23 | NR |
| | | | | Tranexamic acid | 22 | 18 | NR |
| | | | | Lanadelumab | 22 | 0 | NR |

*C1INH,* C1 inhibitor; *IV*, intravenous; *LTP,* long-term prophylaxis; *NA,* not applicable; *NR,* not reported; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *QD*, once daily; *SD*, standard deviation.

[a]Attack severity score was based on a 3-point scale, with 1 indicating mild, 2 indicating moderate, and 3 indicating severe. [b]Presented data are limited to the IV pdC1INH 500 U dose as it is the approved dose for children aged 6 to <12 years.[56] [c]The data were shown graphically by baseline; however, mean and SD values were not reported for LTP. [d]In rollover patients, a single dose of lanadelumab 300 mg was received at study entry and until the patient experienced their first attack, following which the patient received lanadelumab 300 mg Q2W. Non-rollover patients received lanadelumab 300 mg Q2W from study entry onward. [e]Attack severity score was based on a 5-point scale, with 1 indicating very mild; 2, mild; 3, moderate; 4, severe; and 5, very severe. [f]Mean (SD) baseline and on LTP treatment attack severity score among 344 patients receiving attenuated androgens at the time of the survey.

**Table S3. Attack duration in phase 3 randomized placebo-controlled trials**

| First author, year of publication | Duration of treatment | No. of patients | LTP agent and dose | Attack duration, mean (SD) | | |
|---|---|---|---|---|---|---|
| | | | | LTP | Placebo | *P* value |
| Zuraw, 2010 [42] | 2 × 12-weeks | 24 | Cinryze 1000 U every 3-4 days | 2.1 (1.1) days | 3.4 (1.4) days | 0.002 |
| Li, 2019 [41] | 2 × 16-weeks | 90 | Berinert 40 IU/kg twice weekly | 1.8 (1.1) days | 2.1 (1.2) days | NR |
| | | | Berinert 60 IU/kg twice weekly | 1.6 (1.0) days | 1.6 (0.7) days | NR |
| Banerji, 2018 [8] | 26 weeks | 125 | Lanadelumab 150 mg Q4W | 35.6 (24.9) hours | 33.5 (23.4) hours | 0.770 |
| | | | Lanadelumab 300 mg Q4W | 26.0 (21.1) hours | 33.5 (23.4) hours | 0.222 |
| | | | Lanadelumab 300 mg Q2W | 26.6 (22.7) hours | 33.5 (23.4) hours | 0.330 |

*LTP*, long-term prophylaxis; *NR*, not reported; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *SD*, standard deviation.

**Table S4. Attack duration in real-world observational studies**

| First author, year of publication | Study design | No. of patients | LTP agent | Attack duration, mean | | |
|---|---|---|---|---|---|---|
| | | | | Baseline | LTP + on-demand treatment | *P* value |
| Rasmussen, 2016 [37] | Prospective cohort | 6 | Cinryze | 38.7 hours | 20.0 hours | NR |
| **First author, year of publication** | **Study design** | **No. of patients** | **LTP agent** | **Attack duration, median** | | |
| | | | | On-demand therapy only | On LTP treatment | *P* value |
| Aberer, 2017 [36] | Prospective registry (icatibant outcome survey) | 448 | Any LTP agent | 9.0 hours | 8.0 hours | 0.543 |
| | | | C1INH | 9.0 hours | 4.0 hours | 0.041 |
| | | | Androgens | 9.0 hours | 8.0 hours | 0.984 |
| | | | TA | 9.0 hours | 11.6 hours | 0.016 |
| Zanichelli, 2011 [49] | Prospective cohort | 103 | Attenuated androgens | 1.7 days | 1.5 days | NR |
| | | | Antifibrinolytics | 1.7 days | 1.6 days | NR |

*C1INH*, C1 inhibitor; *LTP*, long-term prophylaxis; *NR*, not reported; *TA*, tranexamic acid.

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