PCR144

# Systematic literature review to investigate the impact of hereditary angioedema on health-related quality of life

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## Introduction

- Hereditary angioedema (HAE) is a rare genetic disorder characterised by debilitating, unpredictable and potentially fatal swelling attacks, often in the extremities, stomach, and throat.[1,2]
- HAE has an estimated incidence of 1 in 50,000 people with approximately 15,000 cases in Europe.[2,3]
- HAE attacks result from a C1-INH deficiency or dysfunction, leading to bradykinin overproduction, a potent vasodilator which increases vascular permeability and causes angioedema.[4]
- HAE attacks are associated with disfiguration, severe pain and functional impairment which can reduce work/school productivity and limit education/career achievement.[5,6,7]
- Treatment includes on-demand therapy when attacks occur, or long-term prophylaxis (LTP) to prevent attacks occurring.
- This review examined the existing 26 health-related quality of life (HRQoL) studies for patients with HAE, including randomised controlled trials (RCT) and non-RCTs.

## Objective

- A systematic literature review (SLR) was conducted to identify existing clinical, cost-effectiveness, HRQoL, cost and resource use, and burden of disease studies conducted in HAE; HRQoL results are presented here.

## Methods

- An SLR was conducted in June 2024 to identify HRQoL studies associated with patients with HAE and their caregivers.
- Databases searched included Embase, Medline, Centre for Reviews and Dissemination (CRD) health-technology assessment (HTA) database, EuroQoL database and the ScHARR Health Utilities Database.
- Supplementary grey literature searches were conducted in HTA websites and relevant immunology conferences from the previous two years.
- Studies were relevant if they included patients with HAE ≥12 years old, or their caregivers, and measured HRQoL using HAE-specific or generic assessment tools, or through direct elicitation (Table 1).
- Two independent reviewers assessed each reference based on title and abstract. Full-text copies of all potentially relevant records were obtained and evaluated against the pre-defined selection criteria, in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]
- Data were extracted by one reviewer and verified by a second reviewer.

## Results

- Overall, 5,987 references were screened; 685 references across all research questions underwent secondary screening.
- Of these 685 references, 591 were excluded based on the HRQoL-related selection criteria. As such, 94 unique HRQoL references were included, reporting on 62 unique studies; 26 were full-text papers. This poster considers the 26 full-text papers. (Figure 1).
- Of the 26 full-text papers, treatments assessed included berotralstat (n=4), C1-INH (n=3), donidalorsen (n=2), garadacimab (n=2), danazol (n=1), lanadelumab (n=1), avoralstat (n=1); 12 studies were non-interventional. A placebo arm was included in 11 studies.
- The HAE-specific AE-QoL questionnaire was used in 17 studies. EQ-5D, the preferred HRQoL measure for many HTAs, was reported in only four studies (Figure 2).[9,10,11,12]
- Other tools included the HADS (n=5), SF-36 (n=4), VAS (n=2), SF-12 (n=2), HDI-SF (n=1), HAS (n=1), HAE-BOIS (n=1), AECT (n=1), GAD-7 (n=1), and the SGART (n=1).
- Evidence on the impact of HAE attacks on patients' HRQoL was limited. Only one study, a non-interventional, cross-sectional survey, compared HRQoL during and in between attacks.[10] Mean EQ-5D utility scores were 0.444 for the last HAE attack and 0.722 for in between attacks; the difference was nominal. [10]
- High AE-QoL scores, indicating reduced HRQoL, were observed at baseline and in placebo arms across studies, demonstrating the poor HRQoL among patients with HAE.[13,14,15]
- In many trials, patients with HAE receiving LTP treatment demonstrated HRQoL improvement compared to patients using on-demand therapy alone or no HAE treatment.

9,13,14,16,17,18,19,20,21,22,23,24,25,26,27

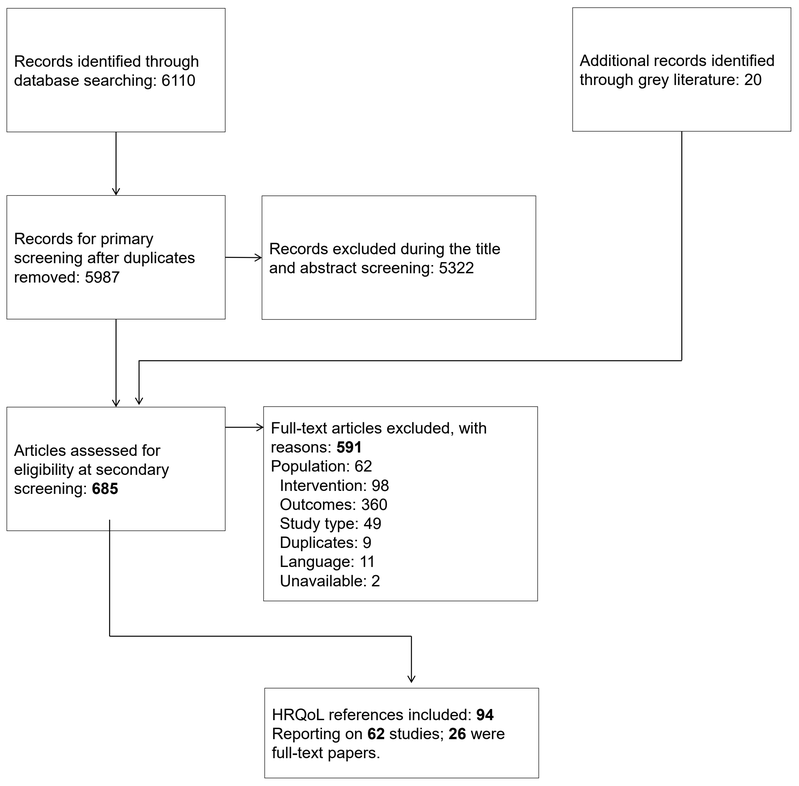
### Table 1: Study selection criteria

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | • Patients with HAE aged 12 years old or above<br>• Carers of patients with HAE | • Studies that include any other patients/populations*<br>• Studies of patients with HAE-nC1INH (Type III) only |
| Interventions/ comparators | • Any intervention, including no intervention, for the treatment of HAE | • No exclusion criteria |
| Outcomes | • HRQoL scores measured using either HAE-specific (e.g. AE-QoL, AECT) or generic tools (e.g. EQ-5D, HUI, SF-6D, CHU-9D), or directly elicited (e.g. TTO) | • No reported outcomes of interest<br>• Proxy questionnaire responses |
| Study type | • RCTs, non-RCTs, observational studies<br>• HRQoL elicitation or validation studies<br>• CEA, CUA, EEACT | • Individual case study reports |

*Unless results for patients with HAE are presented separately

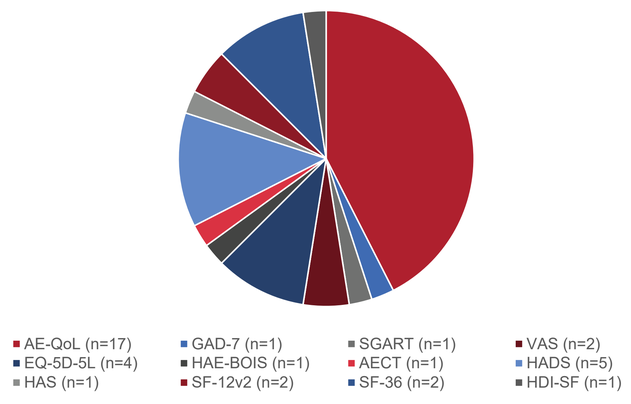
AE-QoL – Angioedema quality of life; CHU-9D – Child Health Utility 9-Dimension; EEACT – Economic evaluation alongside clinical trials; EQ-5D – EuroQoL 5-Dimension; HAE – Hereditary angioedema; HRQoL – Health-related quality of life; HUI – Health Utilities Index; RCT – Randomised controlled trials; SF-6D – Short Form 6-Dimension; TTO – Time trade off

### Figure 1: PRISMA diagram of study selection




HRQoL – Health-related quality of life; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

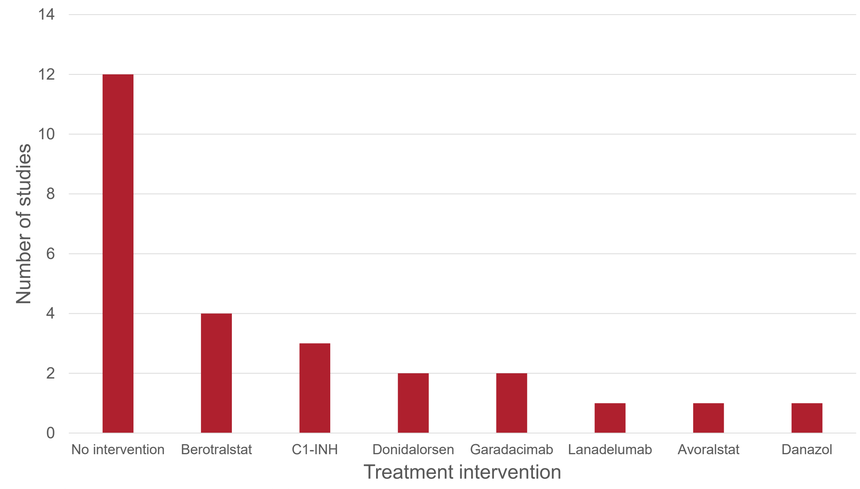
### Figure 2: HRQoL questionnaires used within the SLR (n=26)*




*Some studies used multiple measures to assess HRQoL.

AECT – Angioedema Control Test; AE-QoL – The Angioedema Quality of Life questionnaire; EQ-5D-5L – 5 level EuroQoL scale; GAD-7 – Generalised anxiety disorder 7-item; HADS – Hospital Anxiety and Depression Scale; HAE-BOIS – Hereditary angioedema burden of illness study; HAS – Hospital Anxiety Scale; HDI-SF – Hamilton Depression Inventory-Short Form; HRQoL – Health-related quality of life; SGART – Subject's Global Assessment of Response to Therapy; SF-12v2 – 12 Item short form survey; SF-36 – 36 Item short form survey; VAS – Visual analogue scale

### Figure 3: Treatment interventions assessed within HRQoL studies




HRQoL – Health related quality of life

### Table 2: Summary of AE-QoL results reported

| Author year (Study) | Summary of AE-QoL Score Outcome, intervention/comparator (n): value | | |
|---|---|---|---|
| | Treatment 1 (placebo, where applicable) | Treatment 2 | Treatment 3 |
| Craig 2024 (NCT03712228)[14] | Mean value at baseline and 13 weeks<br>Placebo: 36.6 (19.4); 37.0 (17.3) | Garadacimab 75 mg Q4W: 43.7 (5.9); 14.9 (10.3)<br>Garadacimab 200 mg Q4W: 37.9 (11.2); 17.8 (7.8) | Garadacimab 600 mg Q4W: 40.0 (11.8); 21.0 (16.2)<br>Garadacimab 400 mg Q2W: 56.4 (10.6); 16.5 (7.5) |
| Riedl 2024 (OASIS-HAE)[16] | Total CFB to Week 25, LSM (SE)<br>Placebo (n=43): –4.99 (–11.37 to 1.39) | Donidalorsen 80 mg Q4W (n=45): –17.93 (–24.23 to –11.62) | Donidalorsen 80 mg Q8W (n=44): –20.53 (–27.17 to –13.90) |
| Craig 2023 (VANGUARD)[13] | Mean value at baseline and 6 months<br>Placebo: 45.7; 40.3 | Garadacimab 200 mg monthly: 38.8; 11.7 | |
| Fukuda 2023 (EUdraCT 2019-003921-99)[28] | Mean (SD) change from baseline | C1-INH (SC) 60 IU/kg twice weekly: -24.0 (22.9) | |
| Johnson 2023[15] | Mean score at baseline; 3 months; 6 months | Berotralstat 150 mg daily: 44; 29.14; 22 | |
| Banerji 2022 (HELP)[9, 17, 18, 19] | Total CFB to Week 26, LSM (SE)<br>Placebo (n=37): -4.72 (-10.46 to 1.02) | Lanadelumab 150 mg Q4W (n= 28): -19.82 (-26.76 to -12.88) | Lanadelumab 300 mg Q4W (n=27): -17.38 (-24.17 to -10.58)<br>Lanadelumab 300 mg Q2W (n=26): -21.29 (-28.21 to -14.37) |
| Fijen 2022 (NCT04030598)[25,29] | Mean change from baseline to Week 17<br>Placebo: -6.2 | Donidalorsen 80 mg Q4W: -26.8 | |
| Lo 2022[30] | Mean (SD) total score<br>No intervention: 59.4 (21.9) | | |
| Castaldo 2021[27] | Median (IQR) score:<br>Modelled on-demand-only: 61.8 (44.1–79.4) | All forms of prophylaxis treatment: 41.2 (23.5-57.4)<br>Novel SC prophylaxis treatment: 25.0 (10.3-47.1) | |
| Ohsawa 2021 (APeX-J)[23] | Total CFB to Week 24, LSM (SE)<br>Placebo: 3.18 (6.83) | Berotralstat 110 mg daily: -9.47 (6.93) | Berotralstat 150 mg daily: -15.82 (6.42) |
| Zarnowski 2021[26] | Mean (SD)<br>On-demand: 36.7 (14.9) | Prophylaxis: 24.0 (9.6) | |
| Zuraw 2021 (APeX-2)[21,22] | Total CFB to Week 24, LSM (SE)<br>Placebo: -9.69 (2.64) | Berotralstat 110 mg daily: -12.46 (2.53) | Berotralstat 150 mg daily: -14.59 (2.59) |
| Aygören-Pürsün 2018 (APeX-1)[20] | Total CFB, LSM<br>Placebo (n=23): -4.5 | Berotralstat 125 mg daily (n=14): -29.0 | |
| Riedl 2018 (OPuS-2)[24] | LSM at Week 12<br>Placebo: -12.14 | Avoralstat 300 mg three times daily: -9.89 | Avoralstat 500 mg three times daily: -17.45 |
| Nordenfelt 2017[11] | Median (range) score<br>No intervention: 36.8 (0–91.7) | | |

AE-QoL – The Angioedema Quality of Life questionnaire; CFB – Change from baseline; IQR – Interquartile range; LSM – Least squares mean; Q2W – Every two weeks; Q4W – Every four weeks; Q8W – Every eight weeks; SC – Subcutaneous; SD – Standard deviation; SE – standard error

## CONCLUSIONS

The AE-QoL questionnaire was the most commonly used questionnaire across studies to specifically assesses the impact of HRQoL in patients with HAE. However, there remains difficulty in accurately quantifying the impact of each attack on HRQoL, likely due to the transient and unpredictable nature of attacks.

EQ-5D data, which is the preferred HRQoL measurement by many HTA agencies, did not feature significantly in the findings of the SLR. [31] EQ-5D collected in trials often lacks sensitivity to accurately capture HRQoL decrement directly related to a patient's experience of an HAE attack; literature suggests that the unpredictability of HAE attacks results in misalignment of data collection points to the occurrence of HAE attacks.[32]

Despite a robust SLR, very few studies were identified that captured HRQoL both during and in between patients' HAE attacks.

The findings of the SLR indicate that patients with HAE on LTP treatment demonstrate HRQoL improvement compared to patients using on-demand treatment or on no HAE treatment. This supports LTP treatment as standard of care for patients with HAE.

## FUNDING

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## ABBREVIATIONS

CRD, Centre for Reviews and Dissemination; HAE, Hereditary angioedema; HRQoL, health-related quality of life; HTA, health-technology assessment; LTP, long-term prophylaxis; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials; SLR, systematic literature review; TA, technology assessment

## DISCLOSURES

C. Heeks and M. Thursfield are employees of Otsuka Pharmaceutical Europe Ltd., Windsor, UK. M. Prett, L. Everett, A. Laglia, and B. Kwizera, employees of FIECON, a Herspiegel company, London, UK, received payment from Otsuka Pharmaceutical Europe Ltd. to conduct this research.

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