Title	ICER Observational RWE Pilot: Hereditary Angioedema (HAE)
Protocol version and date	V 2.0, 12 April 2021
Protocol registration or comment period	Manufacturer comment period took place between 5 March 21 through 25 March 21
Study type	Observational study
Objective	To describe baseline demographic characteristics, attack rates, and attack-related medical service utilization among initiators of three HAE treatments for prophylaxis use (Takhzyro, Haegarda, Cinryze).
Country(-ies) of study	United States
Data source	Optum's De-identified Clinformatics® Data Mart
Protocol contributors/ project team	Ashley Jaksa, MPH Scientific Partnerships Lead Aetion, Inc. Krisha Patel, MPH Scientist Aetion, Inc Lisa Bloudek, PharmD, MS Sr. Research Scientist, Department of Pharmacy University of Washington Mandy Patrick, MS Sr Principal Product Scientist Aetion, Inc. Jon Campbell, PhD, MS Senior Vice President, Health Economics Institute of Clinical and Economic Review Josh Carlson, PhD, MPH Associate Professor, Department of Pharmacy University of Washington

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

AEP	Aetion Evidence Platform®
ED	Emergency department
EHR	Electronic health records
FDA	Food and Drug Administration
HAE	Hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
IU	International unit
Kg	Kilogram
RCT	Randomized controlled trial
RWE	Real-world evidence
Rx	Prescriptions

3. Rationale and background

Drugs that receive accelerated approval through the FDA often have uncertainties in clinical and cost-effectiveness at time of launch and subsequent health technology assessment (HTA). ICER is piloting a process to reassess drugs, approved under accelerated pathways, 24 months after its initial assessment. The ICER reassessment will focus on using real-world evidence (RWE) to address uncertainties and update its initial clinical review and cost-effectiveness modeling.

A series of analyses using the Aetion Evidence Platform® (AEP) will be conducted within the Optum's de-identified Clinformatics® Data Mart Database to inform the RWE reassessment.

Results from this analysis and supplemented literature will be used by the University of Washington to provide updated inputs to the original HAE cost-effectiveness model.

4. Research questions and objectives

In the original ICER HAE report, published in November 2018, a number of uncertainties were noted that could substantially impact the cost-effectiveness of the three therapies reviewed:

- Key cost-effectiveness model assumptions were based on data from RCTs (e.g., patients' baseline HAE attack rates), however, 'minor adjustments in key assumptions (e.g., frequency of attacks) could result in substantially different cost-effectiveness results.' How does real-world clinical practice align with the model assumptions derived from the RCTs?
- The FDA label for Takhzyro suggests that patients who remain attack-free for six months may be considered for less-frequent dosing (i.e., one dose every four weeks instead of every two weeks). However, the real-world proportion of patients who will switch to – and remain on – the less-frequent dose is unknown. Less frequent dosing could impact the incremental cost-effectiveness.
- Health care resource utilization and cost inputs were used from published observational studies that were published up to 10 years ago. Revising these estimates with updated RWE could impact the drugs' cost-effectiveness.

The objectives of this observational RWE study are focused on addressing these uncertainties and generating updated cost-effectiveness model inputs. The following research objectives will be addressed:

Primary Objective. Describe baseline demographic characteristics, attack rates, and attack-related medical service utilization among initiators of one of the three treatments for long-term prophylaxis use (Takhzyro, Haegarda, or Cinryze).

- What is the HAE baseline attack rate per month (stratified by severity) in the six months pre-initiation?
- Where is on-demand treatment for acute attacks administered? What is the distribution of specific drugs? How many prescriptions do patients receive?
- For patients with severe attacks, what percent end up hospitalized, and within these patients, what is the utilization of procedures such as cricothyrotomy/tracheotomy, intubation, and artificial respiration?
- What are the costs associated with medical utilization during the acute attack?

Exploratory Objective: Explore attack rates and utilization following long-term prophylaxis initiation.

- What is the severe attack rate per month, post-initiation?
- What percent of patients are attack-free during the follow up period?

- What are the utilization patterns of the prophylactic medications, post initiation?
- What percent of patients receive less frequent dosing for Takhzyro after six months attack free (in line with FDA recommendations)? Do any patients titrate down prior to six months?

5. Research methods

5.1.1.1 Study population

The analysis is specifically focused on patients who are eligible for prophylaxis therapy in line with the target population in the ICER assessment.

5.1.1.2 Prophylaxis initiation cohort for evaluation

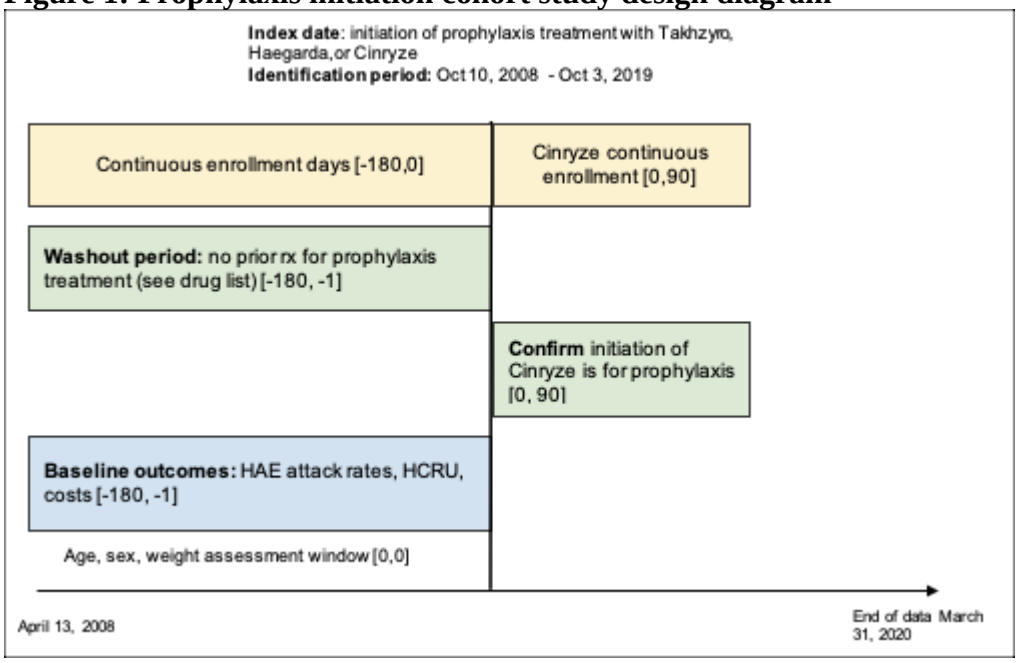
Patients will be eligible to enter the cohort on initiation of Takhzyro, Haegarda, or Cinryze as a prophylactic treatment during October 10, 2008 through October 3rd, 2019 (Figure 1). October 2008 was selected as the start of the study period based on the approval date for Cinryze, the earliest of the medications to be approved. Clinical experts confirmed that 2008 reflects the current treatment paradigm of medications targeting the BK pathway and that all new treatments after 2008 reflect a continual shift away from inferior anabolic androgen therapies. The study period was also selected to maximize sample size for this rare disease.

New use will be defined as no use of Takhzyro or Haegarda, during the 180 days prior (washout period), and no use of Cinryze as a prophylactic treatment during this 180-day washout period. Because Cinryze is used for both acute attacks (off label) and prophylaxis, patients will be excluded based on evidence of prophylactic use of Cinryze (see definition in Annex 2) during the 180 days prior to cohort entry and will be required to have continuous enrollment and evidence of recurring use during the 90 days following cohort entry. Patients receiving other prophylactic treatments (see Annex 1) during the baseline period will also be excluded. Each patient will be included only once, on the first qualifying event. Patients will be required to have at least 180 days of enrollment prior to cohort entry to obtain baseline attack rates.

Using this cohort, we will evaluate baseline outcomes. Patients' demographic characteristics will be assessed at cohort entry. Patients' attack rates, and attack-related medical service utilization and costs will be evaluated.

Note: HAE does not have specific ICD9/10 diagnostic codes. We used initiation of HAE specific treatment to identify patients of interest (i.e., patients with HAE). The method of using HAE treatments to identify HAE patients has been used widely in the literature (Tachdjian 2020, Banerji 2020, Vande Walle 2018).[1-3] In addition, there is no indication that HAE treatments are used off-label for non-HAE patients.

Figure 1: Prophylaxis initiation cohort study design diagram



5.1.1.3 Follow-up cohort for evaluating the exploratory research objective

The goal of the post-initiation exploratory analysis is to evaluate the frequency of attacks after initiation of prophylactic therapy, understand utilization, and determine how many months patients were attack free after initiation. This analysis will not directly influence the cost-effectiveness model; however, there is value in exploring these patient-relevant outcomes in real-world data.

The follow-up cohort will be derived from the baseline cohort. In addition to the baseline cohort inclusion criteria, all patients will be required to have a minimum of 90 days eligibility in the follow-up period. As in the baseline cohort, patients initiating Cinryze will be further required to have recurring use during the 90 days following cohort entry to confirm prophylactic use. Patients will be censored upon maximum follow-up of 365 days, disenrollment, the end of data (March 31st, 2020), or death, whichever comes first. Thus, patients will contribute a minimum of 3 months and a maximum of 1 year of follow-up time to the analysis. A one-year maximum follow-up was selected due to the recency of the Takhzyro approval (August 23rd, 2018).

5.1.1.4 Dose reduction cohort evaluating the exploratory research objective

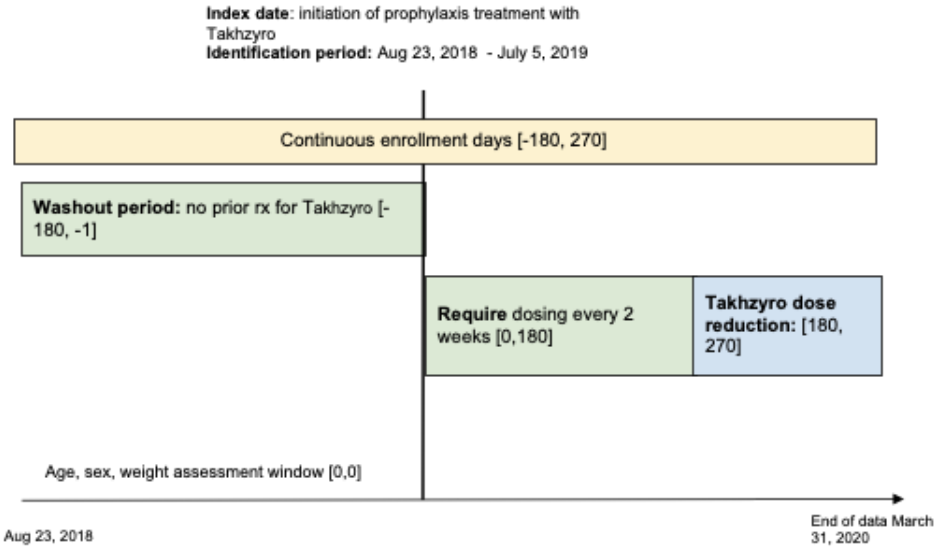
The dose reduction exploratory cohort will only focus on patients initiating Takhzyro.

Patients will be eligible to enter the cohort on initiation of Takhzyro, during August 23, 2018 through July 5, 2019 (Figure 2). August 23, 2018 was selected as the start of the study period based on the approval date for Takhzyro. New use will be defined as no use of Takhzyro, during the 180 days prior to initiation (washout period). Each patient will be included only once, on the first qualifying event. Patients will be required to be continuously enrolled in the 180 days prior to

initiation and for at least 270 days post cohort entry. The FDA label for Takhzyro, states that patients whose attacks are well-controlled for six months should reduce dosing to every four weeks, thus the cohort will require a minimum of six months follow up plus 90 days to establish the new dosing regimen. To be included in the cohort, patients will be required to have dosing, on average, every two weeks during the 180 days post cohort entry.

Using the dose reduction cohort, we will determine the percent of patients that receive the less frequent dosing regimen after six months attack free.

Figure 2: Takhzyro dose reduction study diagram



5.2 Variables

Refer to **Annex 2: Variable definitions** for the definitions of all variables.

5.2.1.1 Patient characteristics

The following patient characteristics will be evaluated on each patient's cohort entry date:

- Age
- Sex
- Weight

For the entire cohort, a list of the top 10 non-HAE therapies used over the baseline period will also be evaluated. We will evaluate the most used therapeutic classes across all patients. In clinical practice, patients may be on additional therapies for comorbidities. Some of these therapies (e.g., estrogens) may be associated with increased risk of HAE attacks.[4] We will provide descriptive information on the most common therapies outside of HAE treatment for patients within the cohort.

Note: weight values may be limited in the Clinformatics® Data Mart. If needed, we will create an additional HAE patient cohort in Optum's De-identified Integrated Claims-Clinical dataset, which combines adjudicated claims data with Optum's Electronic Health Record data, to obtain a larger sample of HAE patients with weight values.

5.2.1.2 Treatment

The main HAE treatments of interest are the prophylactic treatments reviewed in the prior ICER HAE report (see Annex 1 for more details):

- Takhzyro® (lanadelumab, Takeda Pharmaceutical Company, Ltd.)
- Haegarda® (C1 esterase inhibitor [human], CSL Behring, GmbH.)
- Cinryze® (C1 esterase inhibitor [human], Takeda Pharmaceutical Company, Ltd.)

Other on-demand therapies and prophylactic treatments will also be included. In instances where a generic is available, we will include both the brand and generic drug in the analysis.

- Berinert® (C1 esterase inhibitor [human], CSL Behring, GmbH)
- Firazyr® (icatibant, Takeda Pharmaceutical Company, Ltd.)
- Ruconest® (C1 esterase inhibitor [recombinant], Pharming Healthcare, Inc.)
- Kalbitor® (ecallantide, Takeda Pharmaceutical Company, Ltd.)
- Danazol
- Cyklokapron/Lysteda (tranexamic acid)
- Aminocaproic acid
- Oxandrolone
- Methyltestosterone
- Stanozolol

5.2.1.3 Outcome definitions

The following study outcomes are defined below.

5.2.1.4 HAE attack rates

Observational studies that evaluate attack rates in claims or EHR data sets are limited. There is currently no validated method to evaluate HAE attacks in claims data.

In creating our definitions of severe and non-severe attacks, we took guidance from clinical experts, treatment guidelines, and published literature that identified symptoms (Longhurst & Bork 2019)[5] or used diagnoses codes indicative of an attack (Tachdjian 2020).[1] Symptoms and diagnoses codes were cross referenced in a de novo code search to capture both ICD-9 and ICD-10 codes.

Attacks are defined by severity:

- **Severe attack:** Treatment guidelines and empirical data suggest that severe attacks are typically treated in the ED.[6] For this analysis, severe attack will be defined in two ways: broadly as all-cause ED visits with or without hospitalization and more specifically as HAE ED visits with or without hospitalization. HAE specific severe attacks will be defined by a claim for an ED visit with or without hospitalization that includes diagnoses and drugs indicative of an attack (see Annex 2).
- **Non-severe attack**- Non-severe attacks are treated with on-demand therapy either by self-administration or administration by a healthcare professional. An attack treated by a healthcare professional will be defined as a medical service claim for an on-demand therapy occurring outside an inpatient or ED setting (e.g., physician office). For self-administration, we will estimate the number of attacks treated by calculating the number of doses dispensed based on dispensed quantity and approved dosages. Based on treatment guidelines,[6] patients should readily have on-demand therapy to treat two attacks, thus we will consider any doses dispensed over the two on-hand dosages of on-demand therapy as evidence of an attack.

Data on the duration of attacks by severity is limited, however attacks generally last between two and five days.[7] Thus, on-demand therapy administrations by a healthcare professional, ED visits, and inpatient hospitalizations occurring within five days of each other will be considered part of a single attack. In cases where an on-demand therapy administration occurs within five days of an ED visit or hospitalization, the attack will be counted as a severe attack.

5.2.1.5 Costs associated with HAE attacks

Costs will be estimated for HAE attack episodes, by severity and by treatment location (ED only vs inpatient for severe attacks and home versus office for non-sever attacks). Attack costs will be estimated by summing costs across the medical services utilized during an attack, excluding the costs of on-demand therapies, which are included in the cost-effectiveness model separately. Specific outputs will include:

- Outpatient care
    - Cost per attack treated with a home visit for on-demand treatment administration
    - Cost per attack treated with an office visit for on-demand treatment administration
- Cost per attack treated as ED visit
- Cost per attack treated as inpatient hospitalization

If sample size allows, cost analysis will be restricted to most recent years (2017 – 2020) in order to estimate the most timely and relevant costs. This will be a subgroup analysis of the prophylaxis initiation cohort.

5.2.1.6 Costs during baseline

Costs will be estimated during a six-month baseline period prior to prophylaxis initiation. Costs will be reported by place of service and by HAE-related health care utilization (minus HAE drug costs) and all-cause utilization. Specific outputs will include:

- Outpatient care
    - Mean total cost of home visits
    - Mean total cost of physician office visits
- Mean total cost of ED visits
- Mean total cost of inpatient hospitalizations

If sample size allows, cost analysis will be restricted to most recent years (2017 – 2020) in order to estimate the most timely and relevant costs. This will be a subgroup analysis of the prophylaxis initiation cohort.

5.2.1.7 Utilization

HAE and all-cause utilization will be estimated for the following:

- Number of home visits
- Number of office visits
- Number of ED visits
- Number of hospitalizations
- Pharmacy utilization
    - HAE on-demand therapy Rxs and total dose
    - HAE prophylaxis therapy Rxs and total dose, including proportion of days covered per label.
    - Other – number of Rxs

5.2.1.8 Hospitalization utilization

For those patients with severe attacks, defined by inpatient hospitalization or ED visit, we will calculate the percentage of patients hospitalized. Of those hospitalized, we will also estimate utilization for the following:

- Percent of patients receiving cricothyrotomy/tracheotomy
    - Percent that also receive artificial respiration
- Percent of patients intubated
    - Percent that also receive artificial respiration

5.3 Data sources

All analyses will be performed using de-identified administrative claims data without access to personal identifying information. Study findings will contain aggregate data only that cannot be used to identify individual patients.

5.3.1.1 Optum's De-identified Clinformatics® Data Mart

Optum's Clinformatics® Data Mart (CDM) is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The database includes approximately 17-19 million annual covered lives, for a total of over 65 million unique lives over a 9-year period (1/2007 through 12/2019). Clinformatics® Data Mart is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® customer data use agreements.[8,9] CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to health care costs and resource utilization. The population is geographically diverse, spanning all 50 states.

There are 67,691,644 total patients in the data with events spanned January 1, 2007 through March 31, 2020.

Please see Annex 4 for HAE drug coverage policies for United Healthcare.

5.3.1.2 General notes on administrative databases

Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically.[10,11] Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information[12] or prescribing records in outpatient medical records.[13] Drugs used during hospital stays are not recorded in this data source. Prescribing information based on physician notes may overestimate actual medication use because up to 50% of prescriptions are never filled at the pharmacy.[14]

5.4 Statistical analysis

5.4.1.1 Baseline attack rates (primary objective)

Attack rates will be calculated as the total number of attacks in the cohort divided by the number of person-months during baseline (six months prior to initiation of prophylaxis treatment). The rates

and percentages of attacks by severity (severe all-cause, severe-HAE specific, non-severe) will also be calculated for the baseline cohort.

5.4.1.2 Baseline costs (primary objective)

Cost analyses will be based on standard cost amounts reported within the Optum data. Optum's standard costs are based on algorithms that reflect the intensity of care provided, including quantity of services, relative resource costs, and nature of healthcare utilization. Optum's standard costs are an estimate of the allowed amount (i.e., the total cost of the service, and are validated by Optum against the paid amount).[15]

All costs will be inflated to 2021 US dollars using Optum's cost factor tables, if 2021 tables are available (typically released in Q2). This method is recommended for Optum data because costs are standardized in multi-year batches.[15] If 2021 tables are not available, costs will be inflated to 2020 US dollars using Optum's cost factor tables and then inflated to 2021 US dollars using the Personal Consumption Expenditure (PCE) price index.[16]

Mean values will be reported, along with the standard deviation, median, and inter-quartile range.

To assess sensitivity of results to extreme cost values, additional analyses will be performed where cost values are Winsorized,[17] using the 5th and 95th percentile of the cost distribution as cut points. This procedure involves replacing cost values below the 5th percentile with the 5th percentile value and values above the 95th percentile with the 95th percentile value. Thus, extreme values are pulled in, but the weight on the tails of the distribution is maintained.

If sample size allows, cost analysis will be restricted to most recent years (2017 – 2020) in order to estimate the most timely and relevant costs.

5.4.1.3 Exploratory Follow- up descriptive analyses

Due to the small sample size, there is a lack of power to complete a formal pre/post analysis to detect a meaningful difference in attack rates. Thus, our follow-up analysis will be descriptive.

In the follow up period, we are interested in exploring the frequency of attacks after initiation of prophylaxis therapy, understanding utilization, and determining how many months patients were attack free after initiation. Follow up attack rates will be stratified by drug (Takhzyro, Haegarda, and Cinryze) and we will focus on severe attacks only. We will explore the following:

- Adherence to prophylaxis therapy
- Switching behavior between the three prophylaxis drugs
- Attack rates, including attack-free months

5.4.1.4 Sensitivity analyses

We will conduct sensitivity analyses around attack definitions including:

- In our definition of attacks, we considered on-demand therapy administrations by a healthcare professional, ED visits, and inpatient hospitalizations occurring within *five*

days of each other to be considered part of a single attack. We will vary this duration in sensitivity analysis to determine how this impacts attack rates.

- In our definition of non-severe attacks, we assume that patients will have on-demand treatment on hand to treat up to 2 attacks, which is based on treatment guideline recommendations. In sensitivity analysis, we will estimate the number of attacks treated by self-administration without subtracting out two doses to represent drug on-hand.

5.4.1.5 Limitations

There are a number of limitations associated with the proposed analysis:

- The Optum Clinformatics ® Data Mart, which includes over 67 million patients, does not include *all* US patients. The data also represents the policies of the included health plans and might not be representative of *all* US based HAE health plan policies. However, no US based real-world data set reflects all US patients or health plan policies. The Optum Clinformatics ® Data Mart was selected because of its wide patient coverage and availability of criteria (e.g., exposure, outcomes) necessary to complete the analysis.
- There are currently no validated algorithms for measuring attack rates in claims data. We took guidance from clinical experts, treatment guidelines, and published literature for defining severe and non-severe HAE attacks. Please refer to the Model Analysis Plan (MAP) for criteria around use of attack estimates in the model.

5.4.1.6 Software

Results will be generated using the Aetion Evidence Platform® version r4.18. The AEP has been previously validated for a range of studies[17,18] and for predicting clinical trial findings.[19]

6. References

1. Tachdjian R, Johnson K, Casso D, Oliveria S, Devercelli G, Jain G. Real-world cohort study of adult and pediatric patients treated for hereditary angioedema in the United States. *Allergy Asthma Proc.* 2020.
2. Vande Walle S, Starner C, Gleason P. Hereditary Angioedema: A Comprehensive Integrated Medical and Pharmacy Claims Analysis of Utilization and Costs among 15 Million Commercial Insured Members. Paper presented at: AMCP2018; Boston, MA.
3. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Annals of Allergy, Asthma & Immunology.* 2020;124(6):600-607.
4. Banerji A, Riedl M. Managing the female patient with hereditary angioedema. *Womens Health (Lond).* 2016;12(3):351-361.
5. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. *British Journal of Hospital Medicine.* 2019;80(7):391-398.
6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy.* 2018.
7. Cicardi M, Zuraw B. Hereditary angioedema: Treatment of acute attacks. *Uptodate.* 2018. https://www.uptodate.com/contents/hereditary-angioedema-treatment-of-acute-attacks. Accessed June 28 2018.
8. Department of Health and Human Services. 45 CFR 164.514(b)(1). In:2013.
9. US Department of Health and Human Services. Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. 2012.
10. Stergachis AS. Record linkage studies for postmarketing drug surveillance: data quality and validity considerations. *Drug Intell Clin Pharm.* 1988;22(2):157-161.
11. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol.* 2003;10(2):67-71.
12. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol.* 1995;142(10):1103-1112.
13. West SL, Strom BL, Freundlich B, Normand E, Koch G, Savitz DA. Completeness of prescription recording in outpatient medical records from a health maintenance organization. *J Clin Epidemiol.* 1994;47(2):165-171.
14. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med.* 2010;25(4):284-290.
15. Optum Inc. Clinformatics Data Mart User Manual Version 8.0. In:2020.
16. Bureau of Economic Analysis. Table 2.3.6U. Real Personal Consumption Expenditures by Major Type of Product and by Major Function. https://apps.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=2&isuri=1&1921=survey. Published 2021. Accessed February 18, 2021.
17. Weichle T, Hynes DM, Durazo-Arvizu R, Tarlov E, Zhang Q. Impact of alternative approaches to assess outlying and influential observations on health care costs. *Springerplus.* 2013;2:614.

18. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther.* 2016;99(3):325-332.
19. Kim SC, Solomon DH, Rogers JR, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. *Arthritis Rheumatol.* 2017;69(6):1154-1164.
20. Elsevier. Clinical Pharmacology.
21. Centers for Medicare & Medicaid Services, America's Health Insurance Plans, Blue Cross and Blue Shield Association. HCPCS J-Codes. https://hcpcs.codes/j-codes/. Accessed.
22. Riedl MA, Banerji A, Manning ME, et al. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. *Orphanet journal of rare diseases.* 2018;13(1):180-180.
23. Zuraw B, Farkas H. Hereditary angioedema: Acute treatment of angioedema attacks. UpToDate. https://www.uptodate.com/contents/hereditary-angioedema-acute-treatment-of-angioedema-attacks. Published 2020. Updated March 23, 2020. Accessed2021.
24. Zilberberg MD, Jacobsen T, Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. *Allergy Asthma Proc.* 2010;31(6):511-519.
25. Dillon JK, Christensen B, Fairbanks T, Jurkovich G, Moe KS. The emergent surgical airway: cricothyrotomy vs. tracheotomy. *Int J Oral Maxillofac Surg.* 2013;42(2):204-208.
26. Esposito T, Reed R, Adams RC, Fakhry S, Carey D, Crandall ML. Acute Care Surgery Billing, Coding and Documentation Series Part 2: Postoperative Documentation and Coding; Documentation and Coding in Conjunction with Trainees and Advanced Practitioners; Coding Select Procedures. *Trauma Surgery & Acute Care Open.* 2020;5(1):e000586.
27. Pandya S, Baser O, Wan GJ, et al. The Burden of Hypoxic Respiratory Failure in Preterm and Term/Near-term Infants in the United States 2011-2015. *J Health Econ Outcomes Res.* 2019;6(3):130-141.
28. Singh S, Bilal M, Pakhchanian H, Raiker R, Kochhar GS, Thompson CC. Impact of Obesity on Outcomes of Patients With Coronavirus Disease 2019 in the United States: A Multicenter Electronic Health Records Network Study. *Gastroenterology.* 2020;159(6):2221-2225.e2226.
29. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. *JAMA Netw Open.* 2020;3(12):e2029058-e2029058.
30. Banerji A, Busse P, Shennak M, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. *N Engl J Med.* 2017;376(8):717-728.
31. Longhurst H, Cicardi M, Craig T, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. Paper presented at: New England journal of medicine2017.
32. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med.* 2010;363(6):513-522.
33. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. *Vital Health Stat 3.* 2016(39):1-46.
34. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: follow-up survey of US physicians. *J Allergy Clin Immunol Pract.* 2015;3(2):220-227.

35. Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006-2007. *Allergy Asthma Proc.* 2011;32(5):390-394.
36. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol.* 2012;130(3):692-697.
37. Graham C, Supina D, Knox H, Krishnarajah S. Cost Savings Associated With Subcutaneous C1-Inhibitor (Human) Long-Term Prophylaxis for Hereditary Angioedema. *Academy of Managed Care Pharmacy, Dallas, TX, US, October 16-19, 2017.* 2017.
38. Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in the United States, 2004-2007. *Allergy Asthma Proc.* 2011;32(3):248-254.
39. UnitedHealthcare. Takhzyro (lanadelumab-flyo) - Prior Authorization/Medical Necessity - UnitedHeathcare Commercial Plans. https://www.uhcprovider.com/content/dam/provider/docs/public/prior-auth/drugs-pharmacy/commercial/r-z/COMM-PA-Med-Nec-Takhzyro.pdf. Published 2020. Updated September 1, 2020. Accessed March 5, 2021.
40. UnitedHealthcare. Cinryze (C1 esterase inhibitor, human) - Prior Authorization/Medical Necessity- UnitedHealthcare Commercial Plans. https://www.uhcprovider.com/content/dam/provider/docs/public/prior-auth/drugs-pharmacy/commercial/a-g/COMM-Med-Nec-Cinryze.pdf. Published 2020. Updated September 1, 2020. Accessed March 5, 2021.
41. UnitedHealthcare. Haegarda - Prior Authorization/Medical Necessity - UnitedHeathcare Commercial Plans. https://www.uhcprovider.com/content/dam/provider/docs/public/prior-auth/drugs-pharmacy/commercial/h-p/COMM-PA-Med-Nec-Haegarda.pdf. Published 2020. Updated September 1, 2020. Accessed March 5, 2021.

7. Annexes

Annex 1: HAE drugs

Generic	Brand (Administration)	Acute Attack Dose	Long-Term Prophylaxis Dose	How Supplied
C1 Inhibitor, Human (plasma derived C1 inhibitor [pdC1INH])	Cinryze* (IV)	Adults† 1,000 units once. Additional 1,000 units IV if no improvement 60 minutes after first dose. (not studied in children)	Adults &Children ≥12 years 1,000 units every 3-4 days Max Dose: 2,500 units or 100 units/kg every 3 days Children (6-11 years) 500 units every 3-4 days Max Dose: 1,000 units every 3 days Short-Term Prophylaxis† (before a procedure) 20 units/kg or 1,000 units immediately prior to procedure	Cinryze 500 units Powder Vial Reconstitute with 5mL SWFI Concentration: 100 units/mL
	Haegarda* (SC)		Adults &Children ≥6 years 60 IU/kg twice weekly (every 3-4 days)	Haegarda 2000 IU Powder Vial Reconstitute with 4mL SWFI Concentration: 500 IU/mL
				Haegarda 3000 IU Powder Vial Reconstitute with 6mL SWFI Concentration: 500 IU/mL
	Berinert* (IV)	Adults &Children ≥6 year 20 IU/kg once		Berinert 500 IU Power Vial Reconstitute with 10mL SWFI Concentration: 50 IU/mL

Generic	Brand (Administration)	Acute Attack Dose	Long-Term Prophylaxis Dose	How Supplied
Lanadelumab	Takhzyro* (SC)		Adults &Children ≥12 years 300mg every 2 weeks. After 6 months, reduce to every 4-week dosing if patient well-controlled.	Takhzyro 300mg/2mL Solution Vial Concentration: 150mg/mL
C1 Esterase Inhibitor, Recombinant (recombinant human C1 inhibitor [rhC1INH])	Ruconest* (IV)	Adults &Children ≥13 years (non-laryngeal attacks) 50 IU/kg/dose Max Dose: 4,200 IU/dose; 8400 IU per 24 hours	Adults &Children ≥13 years† 50 IU/kg/dose once or twice weekly Max Dose: 4,200 IU/dose once or twice weekly Short-Term Prophylaxis† (before a procedure) 50 IU/kg or 1,000 units immediately prior to procedure	Ruconest 2100 IU Powder Vial Reconstitute with 14mL SWFI Concentration: 150 IU/mL
Ecallantide	Kalbitor* (SC)	Adults &Children ≥12 years 30mg once (administered as three injections of 10mg) Max Dose: 60mg in 24 hours		Kalbitor 10mg/mL Vial Solution for Injection (3 vials per package)
Icatibant	Firazyr (SC)	Adults 30mg once. Repeat administrations in 6-hour intervals. Max Dose: 90mg in 24 hours (EU Pediatric Dosing Weight Based)		Firazyr 30mg/3mL Solution Vial Icatibant 30mg/3mL Solution Prefilled Syringe
Berotralstat	Orladeyo* (Oral)		Adults &Children ≥12 years 150 mg once daily. Adjustment: 110mg once daily for hepatic impairment or GI reactions.	Orladeyo 110mg Capsule Orladeyo 150mg Capsule

Generic	Brand (Administration)	Acute Attack Dose	Long-Term Prophylaxis Dose	How Supplied
Danazol	Danocrine (Oral)		Adults 200 mg twice or three times daily. 100mg every other day also possible. If favorable response after 1-3 months, reduce dose by half. Max Dose: 600mg/day Children >16 years Initially 2.5mg/kg/day (max initial dose: 50mg/day) for ~2 weeks. Then triturate to max tolerated dose and reduce interval to every other day or every third day. Max Maintenance Dose: 5mg/kg/day or 200mg/day Short-Term Prophylaxis† (before a procedure) 2.5 to 10mg/kg/day. Administer 5 days before and 2-3 days after procedure.	Danazol 50mg, 100mg, 200mg Capsule Danocrine 50mg, 100mg, 200mg Capsule
Tranexamic Acid	Cyklokapron Lysteda (Oral)		Adults† 1g twice daily. Adjust dose as needed to between 0.25g and 1.5g twice daily. Max Dose: 3.9g/day Pediatrics† 20mg/kg twice daily. Adjust dose as needed to between 10mg/kg twice daily and 25mg/kg three times daily.	Lysteda 650mg Tablet Tranexamic Acid 650mg Tablet

Generic	Brand (Administration)	Acute Attack Dose	Long-Term Prophylaxis Dose	How Supplied
Aminocaproic Acid	Amicar (Oral)		Adults† First Month: 16g per day, in divided doses every 4-6 hours. Maintenance Dose: 2g three times daily. Adjust dose as needed to between 1g twice daily and 4g three times daily. Max Dose: 36g/day Pediatrics† 0.05g/kg twice daily. Adjust dose as needed to between 0.025g/kg twice daily and 0.1g/kg twice daily.	Amicar 0.25g/mL Oral Solution (236.5 ml bottle) Amicar 500mg, 1000mg Tablet Aminocaproic Acid 0.25g/mL Oral Solution (236.5 ml bottle) Aminocaproic Acid 500mg, 1000mg Tablet
Oxandrolone	Oxandrin (Oral)		Adults† 10mg daily. Adjust dose as needed to between 2.5mg every three days and 20 mg daily. Pediatrics† 0.1mg/kg daily. Adjust dose as needed to between 2.5mg weekly and 7.5mg daily.	Oxandrolone 2.5mg Tablet Oxandrolone 10mg Tablet
Methyltestosterone	Android Methitest Testred Virilon (Oral)		Adult Men† 10mg once daily. Adjust dose as needed to between 5mg every three days and 30mg daily. Not recommended in women and children	Android 10mg Capsule Methyltestosterone 10mg Capsule Testred 10mg Capsule Methitest 10mg Tablet

Generic	Brand (Administration)	Acute Attack Dose	Long-Term Prophylaxis Dose	How Supplied
Stanozolol	Winstrol (Oral)		Adults† 2mg daily. Adjust dose as needed to between 1mg daily and 6mg daily. Pediatrics† 0.5mg daily. Adjust dose as needed to between 0.5mg weekly and 2mg daily.	?

IU = International Units; IV = Intravenous Administration; SC = Subcutaneous Administration; SWFI = Sterile Water for Injection
† = Off-Label Indication; * = Brand-Name Only (Brand Exclusivity); ? = No results in pharmacy databases

Drugs Indicated Only for HAE: Cinryze, Haegarda, Berinert, Takhzyro, Ruconest, Kalbitor, Firazyr, Orladeyo

Annex 2: Variable definitions and code lists

Treatment - Brand Name (Generic)	J Codes and NDCs	Source
Takhzyro (lanadelumab)	J0593 Injection, lanadelumab-flyo, 1 mg (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered) NDCs: 47783-0644-01	Clinical Pharmacology Database[20] and HCPCS[21]
Haegarda (C1 Inhibitor)	J0599 - Injection, HAEGARDA, 10 units (effective Jan 1, 2019) NDCs: 63833-0828-02 63833-0829-02	Clinical Pharmacology Database [20] and HCPCS[21]
Cinryze (C1 Inhibitor)	J0598 - Injection, C1 esterase inhibitor (human), 10 units NDCs: 42227-0081-01 42227-0081-05	Clinical Pharmacology Database [20] and HCPCS[21]
Ruconest (C1 Esterase Inhibitor, Recombinant)	J0596 - Ruconest, 10 units NDCs: 68012-0350-01 68012-0350-02 71274-0350-01 71274-0350-02	Clinical Pharmacology Database[20] and HCPCS[21]
Kalbitor (ecallantide)	J1290 - Injection, ecallantide, 1 mg NDCs: 47783-0101-01	Clinical Pharmacology Database[20] and HCPCS[21]
Berinert (C1 Inhibitor)	J0597 - Injection, C1 Esterase Inhibitor (Human), BERINERT, 10 units NDCs: 63833-0825-02	Clinical Pharmacology Database[20] and HCPCS[21]
Firazyr (icatibant)	J1744 - Injection, icatibant, 1 mg NDCs: 00093-3066-19	Clinical Pharmacology Database[20]

	00093-3066-34 00093-3066-93 24201-0207-01 24201-0207-03 54092-0135-01 54092-0135-02 54092-0702-02 54092-0702-03 60505-6214-01 63323-0574-01 63323-0574-86 63323-0574-93 69097-0664-34 69097-0664-68	and HCPCS[21]
Orladeyo (berotralstat)	Newly approved drug (December 2020) and not available in the analysis data set which runs through March 31st 2020.	
Danazol (Danocrine)	NDCs: 00527-1368-01 00527-1369-01 00527-1369-06 00527-1392-01 00555-0633-02 00555-0634-02 00555-0635-02 00555-0635-09 42291-0243-01	Clinical Pharmacology Database[20]
Cykokapron Lysteda (Tranexamic Acid)	NDCs: 00591-3720-30 55566-2100-01 55566-2110-02 60505-3638-01 60505-3638-03 66993-0090-30 66993-0121-30 69918-0301-30	Clinical Pharmacology Database[20]
Amicar (Aminocaproic Acid)	NDCs: 17478-0447-08 17478-0768-30 17478-0769-30 49411-0050-30 49411-0051-30 49411-0052-08	Clinical Pharmacology Database[20]

	52817-0815-08 60219-1637-03 60687-0505-25 62559-0225-30 66689-0330-08 69238-1596-08 69680-0115-30 69680-0116-30 72205-0049-30	
Oxandrin (Oxandrolone)	NDCs: 49884-0301-01 00185-0271-01 49884-0302-02 00185-0272-60	Clinical Pharmacology Database[20]
Android Methitest Testred Virilon (Methyltestosterone)	NDCs: 00187-0902-01 00115-1408-01 00187-0901-01 00115-7037-01	Clinical Pharmacology Database[20]
Winstrol (Stanozolol)	NDCs: 0024-2253-04??	Clinical Pharmacology Database[20]
Prophylactic use of Cinryze and Ruconest	**Algorithm and code lists**	**Source**
Cinryze prophylactic use	Cinryze is indicated for prophylaxis, but is used off-label for acute attacks. Prophylactic use will be defined as continuous refills of Cinryze averaging ≥1500 IU/week for ≥90 days.	Riedl 2018[22]
Ruconest prophylactic use	Ruconest is indicated for on-demand use, but is used off-label for prophylaxis. Patients with Ruconest prophylactic use will be excluded from the cohort. Prophylaxis use will be defined as continuous refills of Ruconest averaging 50 IU/kg once weekly for 90 days.	Riedl 2018[22]
every four-week	Used to determine if a dose reduction occurred.	

administration of Takhzyro	This will be measured over a 90-day follow-up period based on total dose <= 1200 mg over that period. The 1200 mg is based on three 300 mg injections plus one additional injection to account for potential variation in exact timing.	
Attack severity	**Algorithm and code lists**	**Source**
Severe	ED visit with/without hospitalization, identified based on "Type of service" coded as inpatient or emergency room. Events identified as HAE-specific include at least one of the following diagnose (as a primary diagnosis for hospitalizations /or treatments indicative of an attack: ∉ Codes often associated with HAE: ICD-9-CM 277.6 or ICD-10-CM D84.1 ∉ Angioedema diagnosis: ICD-9-CM 995.1 or ICD-10-CM T78.3* ∉ Administration of on-demand HAE treatment ∉ Diagnosis of swelling, abdominal pain, or asphyxiation: o ICD-9-CM 518.81, 518.84, 787.0*, 782.2, 789.0*, 786.02, 786.05, 786.1 o ICD-10-CM J96.0*, J96.2*, J96.9*, R06.0*, R06.1, R10.*, R11.*, R22.0*, R22.1, R19.0	UpToDate states severe attacks are treated in ED.[23] Tachdjian 2020[1] Zilberberg 2010[24] Longhurst & Bork, 2019
Non- severe attack	Each dose of an on-demand therapy over two acute attack doses is considered an attack. The number of doses dispensed will be calculated from the quantity dispensed and recommended dose and Any on-demand therapy administered outside an inpatient or emergency room setting will be considered a non-severe attack.	
Utilization	**Algorithm and code lists**	**Source**
cricothyrotomy/ tracheotomy	emergency tracheotomy (31603) and an emergency cricothyrotomy (31605)	Dillon 2013[25] Esposito[26]

intubation	The appearance of any of the following encounters CPT - 31500 ICD10 - 09HN7BZ, 0DH57BZ, 0DH58BZ, 0WHQ73Z, 0WHQ7YZ, 09HN8BZ, 0B21XEZ, 0BH13EZ, 0BH17EZ, 0BH18EZ, 0CHY7BZ, 0CHY8BZ ICD9 - 96.04, 96.7x, 96, 96.0,96.5	Pandya 2019[27] Singh 2020[28] De novo code look up
artificial respiration	The appearance of any of the following encounters *Invasive mechanical ventilation*: CPT - 94002, 94003, 94004, 94005, E0472, K0534 ICD10 - 5A1935Z, 5A1945Z, 5A1955Z *noninvasive ventilation*: CPT - 94660, A7027, A7034, A7044, E0452, E0470, E0471, E0601, K0183, K0193, K0194, K0532, K0533 ICD10 - 5A09459, 5A09557, 5A09357, 5A09358, 5A09359, 5A0935B, 5A09457, 5A09458, 5A0945B, 5A09558, 5A09559, 5A0955B ICD9 - 93.90 *ventilation NOS:* CPT- 94656, 94657 ICD10 - 5A0920Z, 5A0945Z, 5A0955Z, 5A19054, 5A0935Z, 5A09358, 5A0935B,	Pandya 2019[27] Singh 2020[28] Rosenthal 2020[29] De novo code look up
Costs	**Algorithm and code lists**	**Source**
Home nurse treatment	Standard cost amount for medical service claims with an on-demand drug administration where the place of service is ‘home’	
Physician office visit	Standard cost amount for medical service claims with an on-demand drug administration where the place of service is ‘office’	
ED visit	Standard cost amount for medical service claims where the type of service is coded as ‘emergency room, professional or facility’	
Hospitalization	Standard cost amount for medical service claims where the type of service is coded as ‘acute inpatient facility’	

Annex 3: Results Table Shells

Table 1: Baseline characteristics of patients with HAE

Characteristic	RWE results	Notes	Prior ICER review base case	Prior ICER review source
Mean age			39.63	Banerji et al. 2017,[30] Longhurst et al. 2017,[31] Zuraw et al. 2010[32]
Female, %			68.4%	Banerji et al. 2017,[30] Longhurst et al. 2017,[31] Zuraw et al. 2010[32]
Mean weight, females			76.4	Fryar et al. 2016[33]
Mean weight, males			88.8	Fryar et al. 2016[33]
List of top 10 non-HAE therapies (therapeutic class)				

Table 2: Attack rates, utilization, and costs in the six-month baseline period before initiation of prophylaxis treatment

Characteristic	RWE results	Notes	Prior ICER review base case	Prior ICER review source
ATTACK RATES AND TREATMENTS ADMINISTERED				
Mean attack rate per month (HAE-specific severe and non-severe)			3.39	Banerji et al. 2017,[30] Longhurst et al. 2017,[31] Zuraw et al. 2010[32]
Number of patients who are attack free in baseline period before starting prophylaxis therapy		Due to drug indications and health plan requirements, this is expected to be minimal or 0.	-	

Distribution of severe attack free months			-	
Proportion of attacks, by severity				
Severe - HAE specific			-	
Severe - All-cause			-	
Non-severe			-	
Treatment administered – Non-severe attacks				
Self			64.9%	Riedl et al, 2015[34]
Home nurse			13.8%	Riedl et al, 2015[34]
Outpatient			21.3%	Riedl et al, 2015[34]
% of severe-HAE specific attacks resulting in hospitalization			40.9%	Zilberberg et al 2011a[35]
% of hospitalized patients receiving cricothyrotomy/ tracheotomy			40.0%	Bork et al[36]
% of cricothyrotomy/ tracheotomy patients who receive artificial respiration			40.0%	Bork et al[36]
% of hospitalized patients who are intubated			60.0%	Bork et al[36]
% of intubated who receive artificial respiration			26.7%	Bork et al[36]
% of attacks treated with these on-demand drugs				Assumption in model
Berinert			25%	
Kalbitor			25%	

Firazyr			25%	
Ruconest			25%	
BASELINE HAE-SPECIFIC COST OUTCOMES				
Costs per home nurse			$179	Graham et al 2017[37]
Costs per physician office visit			$266	Graham et al 2017[37]
Costs per ED visit			$1,796	Zilberberg et al 2011a and 2011b[35,38]
Costs per hospitalization			$5,782	Zilberberg et al 2011a and 2011b[35,38]
BASELINE HAE-SPECIFIC UTILIZATION OUTCOMES				
Average number of home visits			-	
Average number physician office visits			-	
Average number of ED visits			-	
Average number of hospitalizations			-	
Pharmacy – on-demand drug utilization (# of scripts and total dose)			-	

Table 3: Descriptive analysis during follow-up (post initiation of prophylaxis)

Characteristic	Takhzyro initiators	Haegarda initiators	Cinryze initiators*	Notes
Mean age at initiation				
Female, %				

Distribution of severe attack free months				
Mean attack rate per month – severe-HAE specific- follow up period				
Proportion of patients with PDC >80%				
Switching- % patients switching to Takhzyro	N/A			
Switching- % patients switching to Haegarda		N/A		
Switching- % patients switching to Cinyrze			N/A	

*Cinryze patients were required to be adherent to therapy in the 90 days post initiation to determine that they were taking Cinryze prophylactically (versus on-demand use). Takhzyro and Haegarda patients were not required to demonstrate adherence in the 90 days post initiation.

Table 4: Exploratory dose reduction outcomes

Characteristic	Takhzyro initiators	Notes
Percent of Takhzyro patients attack free for 6-month period		
Percent patients on every 4-week dosing for 6 months		
Percent of patients that titrated down to every 2-week dosing		

Annex 4: United Healthcare HAE Drug Coverage Policies

	Takhzyro[39]	Cinryze[40]	Haegarda[41]
Attack rate requirement	At least 1 attack every 4 weeks	Prescriber attests that patient has experienced attacks of a severity and/or frequency such that they would clinically benefit from prophylactic therapy with Cinryze	Prescriber attests that patient has experienced attacks of a severity and/or frequency such that they would clinically benefit from prophylactic therapy with Haegarda

		AND Submission of medical records documenting a history of failure, contraindication, or intolerance to Haegarda (C1 esterase inhibitor, human)	
Reauthorization	Every 8 months	Every 12 months	Every 12 months
Dose changes	If no acute attacks in previous 6 months move to 300 mg every 4 weeks for 12 months	--	--