PROTOCOL SIGNATURE PAGE – TAKEDA STUDY LEAD

Signature: Maureen Watt	**Date:**
Maureen Watt Director, Global Evidence & Outcomes	25 March 2022

Signature: Giovanna Devercelli	**Date:**
Giovanna Devercelli Executive Director, Head Global Evidence & Outcomes, Rare Disease	25 March 2022

Non-Interventional Study Protocol

Title: BURDEN OF HEREDITARY ANGIOEDEMA (HAE) AND IMPACT ON QUALITY OF LIFE: A MULTI-NATIONAL SURVEY OF PATIENTS AND CAREGIVERS

Short title: HAE Multi-national Survey Study (Wave II)

Study ID: 0238-0556

Sponsor: *Takeda*
Thurgauerstrasse 130
8152 Glattpark-Opfikon (Zurich)
Switzerland
Phone: + *044 55 10 00*

Study phase: Post-Approval Company Sponsored (Observational)

Date of version 2.0 **of protocol:** *07MARCH 2022*

1 Administrative Information

1.1 Contacts

Issue	Contact	Contact
Serious adverse event reporting	*Product Complaints*	*PVSafetyAmericas@tpna.com* *Phone: 1-877-825-3327* *E-mail: medicalinformation@tpna.com* *Fax #: 1-800-247-8860*
Takeda Study Lead	*Maureen Watt*	*Phone: +1 617 784 9707* *E-mail: Maureen.watt@takeda.com*
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Scientific Research Lead (carries day-to-day responsibility for the conduct of the study)	*Marie de la Cruz*	*Phone: +1 301-944-6781* *E-mail: marie.delacruz@iconplc.com*

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

<Responsible Medical Officer (Name)> <Credential>, <Department>, <Title>	Date	Local Support Personnel <Credential>, <Department>, <Title>	Date
<Pharmacovigilance Representative (Name)> <Credential>, <Department>, <Title> Drug Safety Officer	Date	<Statistics Representative (Name)><Credential> , <Department>, <Title>	Date
<Others as identified>			

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

<Location of Facility (City, State/Provence)>

<Location of Facility (Country)>

STUDY SUMMARY

<table>
<tr><td>Name of Sponsor(s):
Takeda</td><td>Compound/Product:
Not Applicable</td></tr>
<tr><td colspan="2">Title of Protocol: Hereditary Angioedema (HAE) Multi-national Survey Study (Wave II)</td></tr>
<tr><td>Study Number: 0238-0556</td><td>Phase: Not Applicable</td></tr>
<tr><td colspan="2">Study Design:
This is a non-interventional, cross-sectional, web-based survey of 1) adult (≥18 years of age) patients with a self-reported diagnosis of HAE; 2) caregivers of pediatric patients (≤17 years of age) diagnosed with HAE; and 3) caregivers of adult (≥18 years of age) patients diagnosed with HAE in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.</td></tr>
<tr><td colspan="2">Primary Objectives:
1. To describe adult and pediatric HAE patients' characteristics, including demographics and clinical characteristics.
2. To describe the humanistic burden of HAE on patients and their caregivers
3. To describe the economic burden associated with HAE as experienced by patients and caregivers.

The study will focus on patients in Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.</td></tr>
<tr><td colspan="2">Participant Population: The HAE multi-national survey study will target at least 300 adult persons with a self-reported diagnosis of HAE (type I, II, normal functioning C1-INH, and unknown) and up to 250 caregivers of pediatric HAE patients and up to 200 caregivers of adult HAE patients (type I, II, normal functioning C1-INH, and unknown) combined in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.</td></tr>
<tr><td>Number of Participants:

Patient Survey: N=300 or more
Pediatric Patient's Caregiver Survey: N=250
Adult Patient's Caregiver Survey: N=200</td><td>Study Sites: The study is planned to be conducted in 13 countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.

Data will be collected using one-time web-based surveys of patients with a self-reported diagnosis of HAE and adult and pediatric HAE patients' caregivers. Recruitment in Croatia, Denmark, Hungary, Norway, Poland, Romania, and Sweden will take place primarily via local patient advocacy organizations. Patients and caregivers within Argentina, Brazil, Colombia, Ireland, and Portugal will be recruited by local medical societies.</td></tr>
<tr><td>Dose Level(s):
Not applicable</td><td>Route of Administration:
Not applicable</td></tr>
</table>

Duration of Study:

Overall Study Duration: 20 weeks

Recruitment/Enrolment period: 8 weeks per target country

Treatment/Follow-up: N/A

Criteria for Inclusion:

HAE Patient Survey: Adults (≥ 18 years old) diagnosed with HAE; experienced ≥1 episode of angioedema or prodromal symptoms in the last year; treated with a prescription medication for HAE attack in the last 2 years; able to understand and provide consent; willing to complete a web-based survey; adequate fluency in the target survey language.

Caregiver of a Pediatric Patient Survey: Adults (≥ 18 years old) who provides regular care or support on an unpaid voluntary basis to a child or adolescent (≤ 17 years) diagnosed with HAE; able to understand and provide consent; willing to complete a web-based survey; adequate fluency in the target survey language.

Caregiver of an Adult Patient Survey: Adults (≥ 18 years old) who provides regular care or support on an unpaid voluntary basis to an adult (≥ 18 years old) that was diagnosed with HAE; able to understand and provide consent; willing to complete a web-based survey; adequate fluency in the target survey language.

Criteria for Exclusion:

None

Criteria for Evaluation and Analyses: N/A

Statistical Considerations: Analyses will be primarily descriptive in nature. Results for descriptive analyses will be displayed in tabular format. All programming will be conducted using SAS. Data will be presented appropriately throughout for their distribution: n (%) for categorical data; median (with range or interquartile range, i.e. IQR) for continuous non-normally distributed data; and mean (with standard deviation, i.e. SD, or standard error, i.e. SE) for continuous normally distributed data. These analyses will be presented for the overall sample and by subgroups.

Sample Size Justification: A sample size of up to 400 completed patient surveys is targeted, while sample sizes of 250 per caregiver survey (pediatric and adult) are targeted.

A sample size of 100 individuals would give at minimum (i.e., around a proportion of 0.50) a precision of ±0.098, with a resulting CI width of at most 0.20 (0.40 to 0.60 around an estimate of 0.50). In line with the objectives of the survey, as well as recruitment feasibility assessments, the sample size of at least 400 participants was considered sufficient to provide acceptable levels of precision around the survey estimates (e.g. ±5% around a sample proportion of 0.50) and to allow sufficient power (80%) to detect differences between groups of equal size, which are at least moderate in magnitude (identified as an effect size of 0.50 or greater).

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List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
AECT:	Angioedema Control Test
AE-QoL	Angioedema Quality of Life Questionnaire
BMI:	Body Mass Index
BOIS:	Burden of Illness Study
C1-INH:	C1 Esterase Inhibitor
CA:	Competent Authority
CCSI:	Core Company Safety Information
CI:	Cognitive Interviews
CRF:	Case Report Form
CRO:	Contract Research Organisation
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
HADS:	Hospital Anxiety and Depression Scale
HAE:	Hereditary Angioedema
HRQoL	Health-Related Quality of Life
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LTP:	Long-Term Prophylaxis
PCO:	Patient Centered Outcomes
PSUR:	Periodic Safety Update Report
QA:	Quality Assurance
QOL:	Quality of Life
SAE:	Serious Adverse Event
SADR:	Serious Adverse Drug Reaction
SAP:	Statistical Analysis Plan
SF-12	Medical Outcomes Study Short Form 12-Item Questionnaire

STP: Short-Term Prophylaxis

WPAI-GH: Work Productivty and Activity Impairment Questionnaire-General Health

2 Introduction

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of edema in the face, extremities, trunk, abdomen, genitals, and upper respiratory tract (Bygum et al., 2012; Betschel et al., 2014). Angioedema attacks can be random or occur as the result of trauma. The frequency and duration of attacks can vary. Untreated patients experience attacks every one to two weeks on average, with most episodes lasting three to four days (Bygum et al., 2012, Genetics Home Reference, 2017). HAE is estimated to affect 1 in every 50,000 in the general population (Bygum et al., 2012). Symptoms usually begin in childhood and worsen during puberty; however, 6.1-13.7% of patients may be asymptomatic or have delayed symptom onset (Bygum et al., 2012). The rarity and lack of awareness of the condition often result in delayed diagnosis (Bygum et al., 2012).

HAE is caused by C1 inhibitor deficiency and is categorized into three types depending on the level and function of the C1 inhibitor. HAE Type I is the most common form, representing approximately 85% of cases, and is caused by low antigenic and functional levels of C1 inhibitor. HAE Type II accounts for approximately the remaining 15% of cases and is associated with a normal C1 inhibitor protein level, but impaired function of the protein. The third type of HAE is associated with normal C1 inhibitor function (HAE-nC10INH) and is rare; it's true prevalence and exact pathogenesis are unknown (Betschel et al., 2014; Genetics Home Reference, 2017).

Angioedema attacks are associated with significant cutaneous and abdominal pain, functional impairment, decreased health-related quality of life (HRQoL), and risk of mortality from untreated airway obstruction (Betschel et al., 2014; Malbrán et al., 2014). While increased awareness and understanding of the disease have resulted in more available treatments, there are limited studies that have been conducted examining the humanistic and economic burden of the disease on patients (Bygum et al., 2012, Banerji, 2013). Lumry et al. (2010) assessed burden of illness using a web-based survey that obtained information on attack characterization, treatment, side effects, pain, and functional and emotional burden of disease management. The results showed that patients reported significantly poorer health-related quality of life compared to population norms and that HAE resulted in substantial humanistic burden, including negative impacts on physical health, mental health, education, career, and

work productivity. Bernstein's (2013) survey study reported significant physical and mental impairments, impaired work productivity, high resource utilization, and high prevalence of depression among HAE patients. Caballero, et al. (2014) conducted a novel burden of illness study in Europe (HAE-BOIS-Europe) to obtain a comprehensive picture of HAE from patients in Spain, Germany, and Denmark (HAE-BOIS-Europe). The survey collected information on health care resource utilization, direct and indirect medical costs, impacts on work and school, treatment satisfaction, as well as emotional functioning. Caballero, et al. (2014) found that despite receiving care, HAE patients still experienced frequent and painful attacks, which contributed to substantial physical and emotional impairments during and between attacks. Finally, Banerji et al. (2018) administered paper-based surveys that included items on patient characteristics, burden of disease, and satisfaction with care and treatment options. They found that despite progress on HAE therapies, burden of illness remained high.

The first wave of the multi-national study was administered to HAE patients in seven countries (Australia, Austria, Canada, France, Germany, Spain, Switzerland, and the UK), making it one of the largest studies exploring the humanistic and economic burden of HAE among patients across a large geographical area. These findings from this study were consistent with those found by Bygum et al. (2012), Banerji, et al., (2013), Caballero, et al., (2014), and Lumry et al., (2010). Overall, patients reported that despite the progress and availability of on-demand and prophylactic treatments, HAE attacks continue to be burdensome and negatively affect patients' quality of life and mental wellbeing. Furthermore, HAE impairs work and productivity, with increased attack frequency resulting in greater impairments. Participants reported more severe anxiety and depression as well as greater impairment for HAE-related QoL and these impairments increased with the number of attacks in the past 6 months. The use of emergency medical services remained similar across all attack frequencies.

While there have been increased interest in trying to better understand the burden of illness in HAE in recent years, key gaps in the literature remain, in particular, a comprehensive and multi-national understanding of HAE and its humanistic and economic impacts directly from patients and caregivers. In addition, most surveys have been conducted in high-income

countries thus far; therefore, there still exists an evidence gap as to the burden of HAE in low- and medium-income economies.

2.1 Study Rationale

Takeda is collaborating with ICON's Patient Centered Outcomes (PCO) group to field an observational, cross-sectional, web-based survey aimed at evaluating the burden of HAE and the impact of HAE on patients and caregivers. The patient and caregiver burden surveys will be administered in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden. This study will assess the humanistic and economic burden associated with the management of HAE, in order to create awareness and inform internal decision-making. This study will generate real-world evidence and insights from the perspectives of adult and pediatric patients diagnosed with HAE as well as their caregivers. In addition, the study findings can be used to assess the full value of treatments and support access and reimbursement of appropriate therapies for HAE. By administering the survey in the above countries, Takeda aims to illuminate any differences in the burden of illness across a broader range of the heterogeneous HAE patient population.

3 Study Objective(s) and Endpoint(s)

3.1 Primary Objective(s)

3.1.1 HAE Patient Survey

The primary research objectives for the HAE Patient Survey are:

1. To describe patient characteristics, including demographics and clinical characteristics overall and separately for each subgroup listed below.
2. To describe the patient perspective on the humanistic burden of HAE including: a) disease control (AECT), b) health-related quality of life scores (SF-12 and AE-QoL), and c) psychosocial well-being scores (HADS) overall and for each subgroup listed below.
3. To describe the economic burden associated with HAE as experienced by patients including the direct costs of illness, work productivity and absenteeism (WPAI-GH), treatment history, and health-care resource utilization overall and for each subgroup listed below.

The subgroups that will be examined in the patient survey will include:

- Country
- HAE Type (Type I, II, normal functioning C1-INH, and unknown)
- Number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
- Prophylactic treatment status [Currently on a long-term prophylactic treatment (in total and broken out by prophylactic type) vs. not currently on a long-term prophylactic treatment]
- HADS subscale scores for anxiety and depression (for each subscale, including normal, mild, moderate, and severe)
- AECT Control Category (a score of 10 or above, or below 10)

3.1.2 Caregiver of a Pediatric Patient Survey

The primary research objectives for the HAE Caregiver of a Pediatric Patient Survey are:

1. To describe pediatric HAE patient characteristics, including demographics and clinical characteristics overall and separately for each subgroup listed below.
2. To describe the caregiver perspective on the humanistic burden of HAE on both pediatric patients and caregivers overall and for each subgroup listed below.
3. To describe the economic burden associated with HAE as experienced by caregivers of pediatric patients including the direct costs of illness and work absenteeism overall and for each subgroup listed below.

The subgroups that will be examined in the Caregiver of a Pediatric Patient Survey will include:

- Country
- Age (categorical: <12 years, and 12-17 years)
- Number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)

Prophylactic treatment status [Currently on a long-term prophylactic treatment (in total and broken out by prophylactic type) vs. not currently on a long-term prophylactic treatment]

3.1.3 Caregiver of an Adult Patient Survey

The primary research objectives for the HAE Caregiver of an Adult Patient Survey are:

1. To describe the humanistic burden of caregiving for an adult HAE patient overall and for each subgroup listed below.
2. To describe the economic burden associated with HAE as experienced by caregivers of adult patients including the direct costs of illness and work absenteeism overall and for each subgroup listed below.

The subgroups that will be examined in the Caregiver of an Adult Patient Survey will include:

- Country
- Number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
- Prophylactic treatment status [Currently on a long-term prophylactic treatment (in total and broken out by prophylactic type) vs. not currently on a long-term prophylactic treatment]

The study will focus on patients in the Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.

3.2 Secondary Objectives

The secondary research objectives for the HAE Patient Survey are:

1. To assess the relationship between HAE symptoms and number of attacks, on HRQoL, daily activities, and emotional well-being.
2. To identify demographic and clinical factors that impact quality of life and economic burden for patients with HAE.

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in 13 countries.

This is a non-interventional, cross-sectional, web-based survey of patients with a self-reported diagnosis of HAE and caregivers of HAE patients in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.

Participants in Argentina, Brazil, Colombia, Ireland, and Portugal will be recruited with local medical societies.

In Croatia, Denmark, Hungary, Norway, Poland, Romania, and Sweden, recruitment will take place within local patient advocacy organizations.

The Sponsor will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

Each study site will serve as a point of contact for local participants. The site will provide information about the study and send the survey links to potential participants. Site responsibilities may also vary by country based on local laws and regulations. For example, in countries where wet-ink signatures are required on informed consent documents for participation, the study sites will be responsible for collecting and storing those documents.

4.2 Sponsor Personnel

The Sponsor will keep a record of all relevant sponsor personnel.

4.3 Contract Research Organisation (CRO)

In collaboration with Takeda, ICON, a clinical research organization, is implementing this non-interventional study.

ICON will assume the primary responsibility for the design, conduct, and analysis of the study. In addition to the core project team at ICON, Takeda will collaborate in the review and interpretation of study results. ICON will be responsible for contracting with the patient advocacy organization, medical societies, and healthcare providers that are responsible for recruitment.

ICON will keep a record of all involved personnel.

5 Ethics

This study is a cross-sectional web-based survey study where the existence of the study has no impact on the participant except for collection of informed consent to use of the participant's data.

5.1 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection, including 95/46/EC).

The Sponsor and ICON will ensure that the protocol, any amendments and the Informed Consent Form (ICF) are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

ICON is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

According to applicable regulations, ICON will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the ICF, recruitment messages, the surveys, and other study-related applicable documents.

ICON will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

ICON will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Sponsor with a copy of this list. Copies of the documents will be distributed upon request.

5.3 Authorities

ICON will send required documents to the competent authority (CA) and/or other national, regional or local authorities. The Sponsor or the appointed will keep an updated list of submission and approval dates and a copy of all documents submitted.

5.4 Participant Information and Written Informed Consent

The Site Study Responsible must give the participant written information about the study in a form that the participant can understand, and obtain the participant's consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the particiapnt must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The participant must agree that sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The participant must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The participant has the right to withdraw his/her consent at any time without prejudice. In the ICF it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept.

All ICFs will comply with the Declaration of Helsinki principle and regulatory requirements and be appropriate for this study.

The contents and process of obtaining informed consent will be in accordance with all target countries' applicable regulatory requirements. Informed consent will be obtained before participants are allowed to complete the survey.

For details, see the Informed Consent Form (Appendix B).

6 Study Design and Plan

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a participant to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the participants.
- Quantitative methods shall be used for the analysis of collected quantitative data.

ICON will ensure that End-of-Study notifications are submitted to the concerned authorities and IEC/IRB for the complete study, as locally required.

Based on upcoming knowledge, the Sponsor might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly.

6.1 Discussion of Study Design

This is a non-interventional, cross-sectional, web-based survey of 1) adult (≥18 years of age) patients with a self-reported diagnosis of HAE; 2) caregivers of pediatric patients (≤17 years of age) diagnosed with HAE; and 3) caregivers of adult (≥18 years of age) patients diagnosed with HAE in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden.
Patients will be recruited through health care providers, medical societies, as well as patient advocacy organizations dedicated to serving persons with hereditary angioedema, using a multi-method approach, including telephone, email, website advertisements, and social media postings. Participants will be provided with a brief overview of the study and a link to complete the survey via the web. As feasible, data collection will continue until a maximum of 400 surveys during an expected timeframe of 8 weeks per target country. The data collected will be de-identified.

6.2 Selection of Study Population

6.2.1 Main Patient Survey

The HAE patient survey study will target 300 or more persons with a self-reported diagnosis of HAE (type I, II, normal functioning C1-INH, and unknown) in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden. Approximately 10 to 120 participants will be targeted per country. As HAE prevalence is not available by country, target recruitment numbers will be based on country population (Table 1), in consultation with local experts and representatives of HAEi. Conservative estimates of HAE prevalence are 1 in 50,000 (Bygum, et al., 2012). The target numbers presented are based on consultation described above, and are not presented for the purpose of achieving any specified statistical power which would be needed for advanced statistical analyses.

Table 1. Target HAE patient survey recruitment by country

Country	Population*	Population with HAE*	Target Recruitment†
Argentina	45,195,774	904	40
Brazil	212,559,417	4,251	100
Colombia	50,882,891	1,018	50
Croatia	4,105,267	82	25
Denmark	5,792,202	116	10
Hungary	9,665,710	193	25
Ireland	4,937,786	99	10
Norway	5,421,241	108	10
Poland	37,846,611	757	40
Portugal	10,196,709	204	10
Romania	19,237,691	385	64
Sweden	10,099,265	202	10

*Population numbers from worldometers.info. Population with HAE is estimated based on the best available prevalence data of 1 in 50,000. Proportion of Target Sample is determined by taking Targeted Recruitment and dividing by the desired minimum sample of 300.

† The numbers in this column were arrived at through consultation with HAEi, local KOLs, and local internal resources within Takeda. Further, we hope to achieve 500 participants, which is greater than the 394 total here. While we hope to achieve 500 participants, the 394 total presented here represents what we have been made to expect based on the above consultation.

6.2.2 Caregiver of a Pediatric Patient Survey

The Caregiver of a Pediatric Patient Survey study will target up to 250 caregivers of children and adolescents (≤ 17 years old) with a diagnosis of HAE (type I, II, normal functioning C1-INH, and unknown) in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden. If a caregiver of a pediatric patient is also an HAE patient themselves, they will be able to complete both the patient survey and the caregiver of a pediatric patient survey.

6.2.3 Caregiver of an Adult Patient Survey

The Caregiver of an Adult Patient Survey study will target up to 200 caregivers of adults (≥ 18 years old) with a diagnosis of HAE (type I, II, normal functioning C1-INH, and unknown) in the following countries: Argentina, Brazil, Colombia, Croatia, Denmark, Hungary, Ireland, Norway, Poland, Portugal, Romania, and Sweden. If a caregiver of an adult patient is also an HAE patient, they will be able to complete both the patient survey and the caregiver of an adult patient survey. Caregivers of adults will be recruited through adult participants who take the survey. The adult participant will be asked if they have a caregiver they would like to refer to the study, and be provided with a unique link to send to their caregiver. In this way, the responses of the adult patient and their caregiver can be compared.

6.2.4 Inclusion Criteria

To be eligible for the study, participants will be required to meet all of the following inclusion criteria:

6.2.4.1 HAE Patient Survey

1. Self-reported diagnosis of HAE (Types I, II, normal functioning C1-INH, or unknown type)
2. Age 18 years or older
3. Experienced at least 1 episode of angioedema or prodromal symptoms within the last year
4. Has been treated with a prescription medication for an angioedema attack within the last 2 years
5. Able to understand and provide consent
6. Willing to complete an web-based survey
7. Adequate fluency in the target language in which the survey is designed:

- Spanish (Argentina & Colombia)
- Brazilian Portuguese (Brazil)
- Croatian (Croatia)
- Danish (Denmark)
- Hungarian (Hungary)
- English (Ireland)
- Norwegian (Norway)
- Polish (Poland)
- Portuguese (Portugal)
- Romanian (Romania)
- Swedish (Sweden)

6.2.4.2 Caregiver of a Pediatric Patient Survey

1. A primary caregiver of a child or adolescent who is aged 17 years or younger diagnosed with HAE (Types I, II, normal functioning C1-INH, or unknown type)
    - Primary caregiver means that the individual provides regular care or support on an unpaid voluntary basis. The individual is not a hired professional caregiver.
2. Age 18 years or older
3. Able to understand and provide consent
4. Willing to complete an web-based survey
5. Adequate fluency in the target language in which the survey is designed:
    - Spanish (Argentina & Colombia)
    - Brazilian Portuguese (Brazil)
    - Croatian (Croatia)
    - Danish (Denmark)
    - Hungarian (Hungary)
    - English (Ireland)
    - Norwegian (Norway)
    - Polish (Poland)
    - Portuguese (Portugal)
    - Romanian (Romania)
    - Swedish (Sweden)

6.2.4.3 Caregiver of an Adult Patient Survey

1. A caregiver of an adult who is aged 18 years or older diagnosed with HAE (Types I, II, normal functioning C1-INH, or unknown type)
    - Caregiver means that the individual provides regular care or support on an unpaid voluntary basis. The individual is not a hired professional caregiver.

2. Age 18 years or older
3. Able to understand and provide consent
4. Willing to complete an web-based survey
5. Adequate fluency in the target language in which the survey is designed:
    - Spanish (Argentina & Colombia)
    - Brazilian Portuguese (Brazil)
    - Croatian (Croatia)
    - Danish (Denmark)
    - Hungarian (Hungary)
    - English (Ireland)
    - Norwegian (Norway)
    - Polish (Poland)
    - Portuguese (Portugal)
    - Romanian (Romania)
    - Swedish (Sweden)

6.2.5 Exclusion Criteria

There are no exclusion criteria

6.3 Data Source/Data Collection Process

The source of information for the study will be self-reported data collected from web-based surveys completed by adult HAE patients and caregivers. Participants are members of or referred by patient advocacy organizations, medical societies, or healthcare providers in the target countries.

6.3.1 Enrolment Data

Eligibility and screening data for this study will be retrieved from the web-based screeners presented at the beginning of the patient and caregiver surveys.

6.3.2 Survey Data

Each survey will be administered through an online portal (Confirmit). Localities will be well served with a general, web-based survey hosting on secure servers.

6.3.2.1 HAE Patient Survey

Patient-reported data will be collected via a web-based survey that includes questions on patient clinical characteristics, demographic characteristics, humanistic burden of illness, and economic burden of illness. The survey incorporates validated patient-reported outcome questionnaires in addition to questions focused on ascertaining HAE disease status, frequency of attacks, HAE treatment management, and health care resource utilization. The HAE Patient Survey is organized by the following sections:

1. HAE History and Current Treatment
2. Most Recent Attack - Symptoms and Treatment
3. Patient-Reported Outcomes Instrument (please see the details in section 6.4.3)
    a. Angioedema Control Test (AECT)
    b. Angioedema Quality of Life Questionnaire (AE-QoL)
    c. Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH)
    d. 12-Item Short Form (SF-12 v2.0)
    e. Hospital Anxiety and Depression Scale (HADS)
4. Health Care Resource Utilization
5. General Health & Socio-demographic Information
6. Additional Questions

6.3.2.2 Caregiver of a Pediatric Patient Survey

Data in the Caregiver of a Pediatric Patient Survey will be collected via a web-based survey that includes questions on patient clinical characteristics, humanistic burden of illness on pediatric patients, caregiver impacts, and economic burden of illness. The survey also includes questions focused on ascertaining the pediatric patient's HAE disease status, frequency of attacks, HAE treatment management, and questions related to use of androgens. The Caregiver of a Pediatric Patient Survey is organized by the following sections:

1. Patient Information
2. Patient's Most Recent Angioedema Attack
3. Impacts of HAE on Child/Adolescent Patient
4. Caregiving Information
5. Caregiver Impacts
6. Background & Socio-demographic Information

6.3.2.3 Caregiver of an Adult Patient Survey

Data in the Caregiver of an Adult Patient Survey will be collected via a web-based survey that includes questions on demographic characteristics, patient clinical characteristics,

caregiver impacts, and economic burden of illness. The patient survey is organized by the following sections:

1. Patient Information
2. Caregiving Information
3. Impacts on Caregiver
4. Background and Socio-demographic information

6.3.3 Patient-Reported Outcome Questionnaires

The patient survey will include patient-reported outcome questionnaires described in sections 6.4.3.1-6.4.3.5.

6.3.3.1 Angioedema Control Test (AECT)

The AECT (Weller, et al., 2019) is a questionnaire used to determine the level of disease control in patients with angioedema (Weller, 2019). It consists of four questions with five answer options each. The four questions of the AECT address the frequency of signs and symptoms of the disease (question 1), quality of life impairment (question 2), mental health (question 3), and efficacy of treatment (question 4). Each answer option is awarded 0 to 4 points, from no control (0 points) to complete control (4 points). Thus, a maximum of 4 points per question/answer and a total maximum of 16 points (complete control) can be achieved. The more points patients score, the better their control of the disease. An AECT score of 10 or greater indicates controlled disease. Values of 9 and lower reflect poor control and a need for better treatment (Weller, et al., 2020).

6.3.3.2 Angioedema Quality-of-Life Questionnaire (AE-QoL)

The AE-QoL, a patient-reported questionnaire, was developed to assess quality of life impairments in patients with recurrent angioedema (Weller, et al., 2016). It consists of 17 items regarding the extent to which angioedema has affected the patient's daily life over the last 4 weeks. The measure is self-administered and consists of four dimensions (functioning, fatigue/mood, fears/shame, and nutrition). Table 2 shows the items associated with each scale score, with higher scores indicating increased severity. The AE-QoL is meant to be evaluated

by using its four individual dimensions (profile instrument) but can also be used to determine a total score (index instrument):

The AE-QoL dimension scores as well as the AE-QoL total score are calculated by using the following formula:

(Σ items – min Σ items / max Σ items – min Σ items) x 100

Example:

Dimension "Functioning":

Item 1: answer 3

Item 2: answer 2

Item 3: answer 4

Item 4: answer 5

Σ items: (3+2+4+5) = 14

min Σ items: (1+1+1+1) = 4

max Σ items: (5+5+5+5) = 20

Enter values in formula: (14 - 4 / 20 – 4) x 100 = 62.5%

The AE-QoL dimension scores correspond to the mean of the items within each dimension. If some items are missing, the total of the items within the dimension is divided by the number of the non-missing items. The same holds for the AE-QoL total score. An AE-QoL dimension score should not be calculated if more than one item is missing in that dimension. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are missing. Please note that only calculating the raw dimension scores (mean of the item scores within each scale) and the raw total score (mean of all item scores) would be easier than the above described procedure. However, in case of missing answers, an inter-individual as well as an intra-individual comparison of AE-QoL results would be limited. The above described linear transformation of all raw scores into percentage scores (indicating the location of the raw scores in relation (in percent) to its maximum possible score) solves this problem and makes it possible to judge and compare AE-QoL results even when single items are missing. The linear transformation of raw scores results in minimal and highest possible scale and total scores of 0 and 100, respectively.

Table 2. Scoring the AE-QoL

Dimensions and Total Score	Number of Items	Score Range	Item Numbers
Functioning	4	4 to 20	1, 2, 3, 4
Fatigue/Mood	5	5 to 25	6, 7, 8, 9, 10
Fears/Shame	6	6 to 30	12, 13, 14, 15, 16, 17
Nutrition	2	2 to 10	5, 11
Total score	17	17 to 85	1 to 17

6.3.3.3 Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH)

The Work Productivity and Activity Impairment—General Health (WPAI–GH) is a self-administered questionnaire (Reilly et al., 1993) comprising six questions that measure the effect of health problems on participants' ability to work and participate in regular activities based on their experiences in the previous 7 days. The WPAI–GH includes four domains (absenteeism, presenteeism, work productivity loss, and activity impairment). All participants are asked whether they are employed (Q1) and about the degree their health problems affect regular activities (Q6). Employed participants are asked about hours of work missed due to health problems (Q2), hours of work missed due to other reasons (Q3), hours actually worked (Q4), and the degree health problems affected their productivity while working (Q5).

Responses to the items are scored to produce the following four domains:

- Absenteeism: work time missed due to health problems = Q2/(Q2+Q4)
- Presenteeism: impairment while working due to health problems = Q5/10
- Work Productivity Loss: overall work impairment due to health problems = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Activity Impairment: activity impairment due to health problems = Q6/10

Each score is then multiplied by 100 to express domains in terms of impairment percentages, with higher numbers indicating greater impairment and less productivity (i.e., worse outcomes). If an item contributing towards a score is missing, the score will not be calculated.

6.3.3.4 Medical Outcomes Study Short Form 12-Item Questionnaire (SF-12)

The SF-12 version 2.0 is a generic quality-of-life questionnaire, which includes 12 items that assess general health, physical functioning, role functioning due to physical health problems, role functioning due to emotional problems, pain, vitality, mental health, and social functioning (Ware, Kosinski, & Keller, 1996). The 1-week recall version is included in the survey. Optum's certified scoring service will be used to score the SF-12. The norm-based physical component summary (PCS-12) and mental component summary (MCS-12) scores derived from the questionnaire will be summarized along with the normalized individual item responses. Lower scores indicate worse health status. In normative data, the mean score is set to 50. Scores >50 indicate better physical or mental health than the mean, while scores <50 indicate worse physical or mental health than the mean.

The scoring algorithm used to score the SF-12v2 usually allows for calculation of a score despite some missing items. The Full Missing Score Estimation method allows for estimation of missing items if one item in a two-item domain is present, prior to use of the standard scoring algorithm. If an item is missing from a single-item domain, a different scoring algorithm will be used, appropriate for the domain with the missing item in question. The Maximum Data Recovery allows PCS and MCS scores to be estimated when there is data for at least seven of the eight domains and there are no missing items for the following domains: PF for the calculation of the PCS score and MH for the calculation of the MCS score (Ware, et al., 1996).

6.3.3.5 Hospital Anxiety and Depression Scale (HADS)

The 14-item HADS (Zigmond & Snaith, 1983) is widely used as a screening tool to detect states of anxiety and depression in a general hospital setting. A review of the literature on the validity of the HADS indicates that it is a widely used questionnaire in assessing symptom severity and depression in somatic, psychiatric, and primary care patients, as well as in the

general population (Hermann, 1997). Prior research (Zigmond & Snaith, 1983) has found that 38% of HAE patients experience anxiety, and 14% experience depression, while the prevalence of each in general population is only 10% [Kessler, et al., 2005) and 6.7% (Kessler, et al., 2009) respectively. The scale assesses how the patient has been feeling in the past week and includes 7 items related to anxiety (odd numbered) and 7 items related to depression (even numbered). Items are scored from 0 (less distress) to 3 (greater distress). Anxiety and depression subscale scores range from 0 to 21, with higher scores indicating a worse state. Scores for each subscale (anxiety and depression) are categorized as follows: normal 0-7, mild 8-10, moderate 11-14, and severe 15-21 (Snaith, 2003). For each subscale, if one item response is missing, the response will be imputed as the mean of the remaining six items (Bell, et al., 2016). If more than one question is missing, the subscale is set to missing. A total score is composed of the sum of the anxiety and depression subscales.

6.3.4 Schedule of Assessments

This is an observational study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. The surveys are one-time, web-based surveys. The HAE Patient Survey is expected to take 45-minutes, the Caregiver of a Pediatric Patient Survey is expected to take 30-minutes, while the Caregiver of an Adult Patient Survey is expected to take 20-minutes.

Caregivers with more than one child with HAE are able to complete the Caregiver of a Pediatric Patient Survey more than once. Caregivers with more than one child will be instructed to complete entire survey with the eldest child in mind. Upon completion of the survey, the caregiver will be provided with a unique link. The link will lead to an abridged version of the survey that will only include the following sections:

- Patient Information
- Patient’s Most Recent Angioedema
- Impact of HAE on Child/Adolescent Patient

6.4 Definitions of Study Variables

6.4.1 Outcome/Endpoint Variables

6.4.1.1 Patient Survey

The patient survey includes items in the following content areas:

- Demographic characteristics (e.g., age, sex, education level, marital status, insurance type (if applicable), residence, employment status)
- Clinical and disease characteristics (e.g., HAE type, age at onset and diagnosis, family history, HAE symptoms; frequency of attacks; and duration, severity, and location of the most recent angioedema attack).
- Individual economic burden of illness including direct costs of illness, work productivity and absenteeism, treatment history, and health-care resource utilization.
- Information on humanistic burden of illness, including health-related quality of life.

Table 3. HAE Patient survey variables to be used in the analyses

Variable	Type
Subject ID	Continuous variable
Country	Categorical variable
Age	Continuous variable
Gender	Dichotomous variable
Race	Categorical variable
Marital status	Categorical variable
Insurance type	Categorical variable
Residence	Categorical variable
Education	Ordinal variable
Employment status	Categorical variable
Type of health insurance	Categorical variable
Household income	Ordinal variable
HAE type	Categorical variable
Age at onset (years)	Continuous variable
Age at diagnosis (years)	Continuous variable
Number of doctors seen	Continuous variable
Family History	Categorical variable
Family History of Suffocation	Categorical
Frequency of attacks	Continuous variable
Duration of most recent attack	Ordinal variable

Severity of most recent attack	Ordinal variable
Location of most recent attack	Categorical variable
Current long-term prophylactic use	Dichotomous variable
Duration of long-term prophylactic treatment	Ordinal variable
Current long-term prophylactic treatment	Categorical variable
Frequency of long-term prophylactic treatment	Ordinal variable
Current short-term prophylactic use	Dichotomous variable
Current short-term prophylactic treatment	Categorical variable
Past long-term prophylactic use	Dichotomous variable
Past long-term prophylactic treatment	Categorical variable
Reasons for discontinuing past long-term prophylactic	Categorical variable
Past short-term prophylactic use	Dichotomous variable
On-demand treatment history	Categorical variable
HAE disease control	Ordinal variable
Treatment control	Categorical variable
Treatment satisfaction	Ordinal variable
Treatment convenience	Ordinal variable
Use of diary	Dichotomous variable
Type of diary used	Categorical variable
Experienced [Androgen] side effects	Categorical variable
Types of [Androgen] side effects	Categorical variable
[Androgen] side effects severity	Ordinal variable
[Androgen] side effects costs	Categorical variable
Type of HCP seen	Categorical variable
Frequency of HCP visits	Continuous variable
Direct cost of illness	Categorical variable
Frequency of healthcare visits	Continuous variable
AECT frequency of angioedema score	Continuous variable
AECT quality of life impairment score	Continuous variable
AECT mental health score	Continuous variable
AECT efficacy of treatment score	Continuous variable
AECT Total score	Continuous variable
AE-QoL Functioning score	Continuous variable
AE-QoL Fatigue/Mood score	Continuous variable
AE-QoL Fears/Shame score	Continuous variable
AE-QoL Nutrition score	Continuous variable
AE-QoL Total score	Continuous variable
WPAI-GH absenteeism	Continuous variable

WPAI-GH presenteeism	Continuous variable
WPAI-GH work productivity loss	Continuous variable
WPAI-GH activity impairment	Continuous variable
SF-12 vitality score	Continuous variable
SF-12 physical functioning	Continuous variable
SF-12 bodily pain	Continuous variable
SF-12 general health perceptions	Continuous variable
SF-12 physical role functioning	Continuous variable
SF-12 emotional role functioning	Continuous variable
SF-12 mental health	Continuous variable
SF-12 social functioning	Continuous variable
SF-12 physical health component	Continuous variable
SF-12 mental health component	Continuous variable
HADS anxiety subscale	Continuous variable
HADS depression subscale	Continuous variable
HADS emotional distress subscale	Continuous variable

6.4.1.2 Caregiver of a Pediatric Patient Survey

The Caregiver of a Pediatric Patient Survey includes items in the following content areas:

- Patient Information (e.g., child age, child gender, HAE type, age at onset and diagnosis; number of doctors seen for diagnosis; distance to HAE provider, number of attacks in the past six months, areas affected by an attack, long-term prophylaxis (LTP) use, LTP type, LTP use duration, LTP frequency, LTP perceived control; androgen side effects experience, androgen side effects treatment costs, on-demand medication use, on-demand medication type, number of mild angioedema attacks in the past six month, patient comorbid conditions)
- Most Recent Angioedema Attack (e.g., Time of most recent attack; frequency of attacks; duration and location of the most recent angioedema attack; types of assistance caregiver provided during child's most recent attack).
- Impacts of HAE on Child/Adolescent Patient (e.g., impacts on daily activities, physical activities, ability to take part in hobbies/sports, social activities, emotions (sadness, feeling down, anger, anxiety, fear), sleep, and school).
- Caregiving Information (e.g., shared household, number of people in household diagnosed with HAE, types of help generally provided to child, days per month

providing care, use of professional/hired caregiver, use of diary to record attacks, type of diary used to record attack)

- Caregiver Impacts (e.g., impacts on daily activities, impacts on daily activities before LTP, impacts on normal daily activities, impacts on emotions, impacts on emotions during COVID-19 pandemic; impacts on social activities, sleep, personal time, relationships, plans; use of support resources).
- Economic burden of illness including direct costs of illness and work absenteeism.
- Background and Socio-demographic information (e.g., gender, HAE diagnosis, caregiver co-morbid conditions, employment status

Table 4. Caregiver of a Pediatric Patient Survey variables to be used in the analyses

Variable	Type
Subject ID	Continuous variable
HAE Status	Dichotomous variable
HAE type	Categorical variable
Caregiver Age	Continuous variable
Child's Age	Continuous variable
Country	Categorical variable
Child's Gender	Categorical variable
Age at onset (years)	Continuous variable
Age at diagnosis (years)	Continuous variable
Doctor's seen for diagnosis	Continuous variable
Length of travel to HAE HCP	Categorical variable
Frequency of attacks	Continuous variable
Attack Areas	Categorical variable
Current long-term prophylactic use	Categorical variable
Duration of long-term prophylactic treatment	Ordinal variable
Current long-term prophylactic treatment	Categorical variable
Frequency of long-term prophylactic treatment	Ordinal variable
LTP Control	Ordinal variable
Experienced [Androgen] side effects	Categorical variable
Types of [Androgen] side effects	Categorical variable
[Androgen] side effects severity	Ordinal variable
[Androgen] side effects costs	Categorical variable

On-demand use	Categorical variable
On-demand treatment	Categorical variable
Number of mild attacks in the past 6 months	Continuous variable
Child's comorbid conditions	Categorical variable
Timing of most recent attack	Ordinal variable
Duration of most recent attack	Ordinal variable
Symptoms of most recent attack	Categorical variable
Severity of most recent attack	Ordinal variable
Types of assistance provided during most recent attack	Categorical variable
Child's daily activity impacts	Categorical variable
Child's physical activity impacts	Categorical variable
Child's impacts hobbies/sports	Categorical variable
Child's social activity impacts	Categorical variable
Child's sadness/feeling down	Categorical variable
Child's anger	Categorical variable
Child's anxiety or fear	Categorical variable
Child's sleep impacts	Categorical variable
Child's missed school days	Categorical variable
Child's lateness/early dismissal	Categorical variable
Shared household	Dichotomous variable
Number of people in household with HAE diagnosis	Continuous variable
Types of help provided to child	Categorical variable
Number of days per month providing care	Continuous variable
Use of professional/hired caregiver	Categorical variable
Use of diary for attacks	Dichotomous variable
Type of diary used	Categorical variable
Caregiver impact on daily activities	Categorical variable
Caregiver impact on daily activities pre-LTP	Categorical variable
Caregiver impact on normal activities	Categorical variable
Caregiver impact on social activities	Categorical variable
Caregiver emotional impacts	Categorical variable
Caregiver emotional impacts worsened by COVID-19	Categorical variable
Frequency of feeling sad/down	Ordinal variable
Time spent worrying or stressing	Ordinal variable
Impacts on caregiver's sleep	Ordinal variable
Caregiver's amount of personal time	Ordinal variable
Caregiver difficulties with relationships	Categorical variable
Impacts on caregiver plans	Categorical variable

Caregiver use of social resources	Dichotomous variable
Use of social resources in the past four weeks	Dichotomous variable
Impacts on work/volunteering	Categorical variable
Caregiver's time missed from work	Categorical variable
Out-of-pocket expenses	Ordinal variable
COVID-19 impacts on caregiving responsibilities	Categorical variable
Caregiver's gender	Categorical variable
Caregiver's HAE status	Dichotomous variable
Caregiver's comorbidities	Categorical variable
Caregiver's employment status	Categorical variable
Caregiver's marital status	Categorical variable

6.4.1.3 Caregiver of an Adult Patient Survey

The patient survey includes items in the following content areas:

- Patient Information (e.g., Patient's gender, frequency of attacks in the past six months, current LTP status, comorbid conditions)
- Caregiving Information (e.g., relationship to patient, shared household status, length of time caregiving, types of assistance provided, days per month providing care, days per month providing care prior to LTP use, use of professional/hired caregiver, types of assistance provided during most recent attack)
- Impacts on Caregiver (e.g., Impacts on daily activities, impacts on daily activities prior to LTP use, impacts on normal daily activities, impacts on social activities, emotional impacts, emotional impacts affected by COVID-19, feeling sad or down, time spent worrying/stressing, sleep impacts, impacts on personal time, relationship impacts, impacts on plans, use of social resources, use of social resources in the past four weeks, impacts on work productivity, work absenteeism, costs related to child's HAE care, and COVID-19 impacts on caregiving responsibilities)
- Background and Socio-demographic characteristics (e.g., age, sex, education level, marital status, employment status, and comorbid conditions)

Table 5. Caregiver of an Adult Patient Survey variables to be used in the analyses

Variable	Type
Subject ID	Continuous variable
HAE type	Categorical variable
Caregiver Age	Continuous variable
Patient's Age	Continuous variable
Country	Categorical variable
Patient's Gender	Categorical variable
Frequency of attacks in the past six months	Continuous variable
Current long-term prophylactic use	Categorical variable
Patient's comorbid conditions	Categorical variable
Relationship to patient	Categorical variable
Shared household	Dichotomous variable
Number of people in household with HAE diagnosis	Continuous variable
Length of time caregiving	Continuous variable
Types of assistance provided	Categorical variable
Days per month caregiving	Continuous variable
Days per month caregiving prior to LTP	Continuous variable
Use of professional caregiver	Categorical variable
Help provided during most recent attack	Categorical variable
Caregiver impact on daily activities	Categorical variable
Caregiver impact on daily activities pre-LTP	Categorical variable
Caregiver impact on normal activities	Categorical variable
Caregiver impact on social activities	Categorical variable
Caregiver emotional impacts	Categorical variable
Caregiver emotional impacts worsened by COVID-19	Categorical variable
Frequency of feeling sad/down	Ordinal variable
Time spent worrying or stressing	Ordinal variable
Impacts on caregiver's sleep	Ordinal variable
Caregiver's amount of personal time	Ordinal variable
Caregiver difficulties with relationships	Categorical variable
Impacts on caregiver plans	Categorical variable
Caregiver use of social resources	Dichotomous variable
Use of social resources in the past four weeks	Dichotomous variable
Impacts on work/volunteering	Categorical variable
Caregiver's time missed from work	Categorical variable
Out-of-pocket expenses	Ordinal variable
COVID-19 impacts on caregiving responsibilities	Categorical variable
Caregiver's gender	Categorical variable

Caregiver's HAE status	Dichotomous variable
Caregiver's comorbidities	Categorical variable
Caregiver's employment status	Categorical variable
Caregiver's marital status	Categorical variable

6.5 Study Setting

HAE patients and caregivers in Argentina, Brazil, Colombia, Ireland, and Portugal will be recruited with local medical societies.

In Croatia, Denmark, Hungary, Norway, Poland, Romania, and Sweden, recruitment will take place within local patient advocacy organizations.

The HAE Patient Survey target sample will include approximately 10 to 120 participants per target country. The Caregiver of a Pediatric Patient Survey and the Caregiver of an Adult Patient Survey will target n=250 and n=200 participants, respectively.

The estimated sample size is considered sufficient to evaluate the key disease impacts experienced by HAE patients and caregivers. The following steps will be undertaken to recruit survey participants, as feasible:

- Patient Advocacy Organization (All countries, excluding Ireland and Portugal)
    - Advertisements about study on patient advocacy organizations' websites.
    - Invite all members of the patient advocacy organizations' databases to participate via email and mail.
    - Social media postings
    - Telephone outreach
    - Word of mouth
- Medical Societies (Argentina, Brazil, Colombia, Ireland, and Portugal)
    - Invitations via email and mail.
    - Social media postings
    - Telephone outreach
    - Word of mouth

6.6 Study Procedures

6.6.1 Recruitment

6.6.1.1 Patient Advocacy Organizations

Patient advocacy organizations based in Croatia, Denmark, Hungary, Norway, Poland, Romania, and Sweden will recruit patients and caregivers in their respective countries. Patient advocacy organizations in the target countries may advertise the study on their website and social media, contact (via email or phone) members in their database, or use word-of-mouth referrals.

Appendix A presents study advertisements and invitations that may be posted or sent to potentially eligible patients with HAE and their caregivers. The advertisement will include a brief overview of the study and a link to complete the surveys via the web.

The patient advocacy organizations will send out reminders via email, social media posts, and other online posts to their members throughout the recruitment period to inform members that the surveys are still open, and that they can disregard the messages if they have already completed the surveys.

6.6.1.2 Medical Societies

Medical societies based in Argentina, Brazil, Colombia, Ireland, and Portugal will recruit patients and caregivers in their respective countries. The medical societies in the target countries may advertise (Appendix A) the study on their website and social media, contact (via email or phone) members in their database, or use word-of-mouth referrals.

6.6.1.3 Healthcare Provider (HCP) Recruitment

The HCPs will refer potential participants to the appropriate survey links.

6.6.2 Participant Selection

Patient advocacy organizations and medical societies will recruit members for participation in the survey using study advertisements or invitations provided by ICON. The recruitment messages (Appendix A) will include a brief overview of the study and a link to complete the survey via the web.

6.6.3 Participant Enrolment

Patients and caregivers who access their respective survey links will first answer study eligibility questions via a web-based screener (Appendix C-E). For those who are confirmed eligible, they will be presented with an IRB/IEC-approved electronic ICF (Appendix B). Eligible patients and caregivers will only be included in the study after providing their consent electronically. Informed consent will be obtained before participants are allowed to complete the survey.

Completion of the HAE patient survey (Appendix C-E) is expected to require up to 45 minutes of the participant's time, while the Caregiver of a Pediatric Patient Survey and the Caregiver of an Adult Patient Survey are expected to require up to 30 and 20 minutes, respectively. Participants must complete the survey in one sitting. Recruitment messages and reminders will be disseminated throughout the recruitment period to inform individuals that the surveys are still open, and that they can disregard the messages if they have already completed the surveys. Patients and caregivers will have the ability to opt-out of the survey if they are not interested in participating.

6.6.4 Screen Failures

Only participants who meet all eligibility criteria on the web-based screener and provide consent will be permitted to participate in the study. Limited data (i.e., age, reason[s] for screen failure [refused consent or ineligible]) will be collected. This will provide an opportunity to make a comparison between participants who are enrolled into the study and those who did not meet all inclusion and eligibility criteria.

6.6.5 Participant Completion of the Study

Participants should be included in the study only once. Data erroneously collected from participants without electronic consent will not be included in or will be deleted from the database.

A survey is considered completed if the participant answered all required questions. The survey will not progress unless a response is provided to a required question. Upon completion of the survey, the participant will be provided with a unique completion code. The participant will email the completion code to their country-specific patient advocacy, professional organization, medical society, or healthcare provider (Ireland and Portugal), which will then confirm the code with ICON. Upon confirmation, the patient advocacy organization, medical society, or healthcare providers will remunerate participants for the completion of the survey, per the following:

- HAE Patient Survey: An equivalent of $45 USD
- Caregiver of a Pediatric Patient Survey
    - First completion: An equivalent of $30 USD
    - Subsequent completions: An equivalent of $15 USD
- Caregiver of an Adult Patient Survey: An equivalent of $30 USD

6.6.6 Participant Withdrawal from the Study

Participants may decline participation and withdraw from the study at any time. Compensation will only be provided to participants who complete the survey.

6.7 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

6.8 Premature Termination or Suspension of Study or Investigational Site

6.8.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.
- If ICON (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.8.2 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study, study-specific procedures for early termination or suspension will be provided by the sponsor; the procedure will be followed by ICON during the course of termination or study suspension.

6.9 Study Plan

Table 6: Data collection overview

	Time point #1: Patient Survey Completion	**Time point #1: Caregiver of a Pediatric Patient Survey Completion**	**Time point #1: Caregiver of an Adult Patient Survey Completion**
Informed consent	x	x	x
Web-based screening (Inclusion/exclusion criteria)	x	x	x
HAE Patient Survey	x		
Caregiver of a Pediatric Patient Survey		x	
Caregiver of an Adult Patient Survey			x
Angioedema Control Test (AECT)	x		
Angioedema Quality of Life Questionnaire (AE-QoL)	x		
Work Productivity and Activity Impairment	x		

Questionnaire: General Health v2.0 (WPAI:GH)			
12-Item Short Form (SF-12 v2.0)	x		
Hospital Anxiety and Depression Scale (HADS)	x		

7 Safety Reporting

7.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.
Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the participant/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the participant/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the participant/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Occupational exposure

- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

Relationship of an AE to studied drug(s)

- **Related (Yes):** An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), or for which a casual relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- **Not related (No):** An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments. The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator’s assessment.:

7.2 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

SAEs, AEs, ADRs, SSRs and PQIs in the medical record/source data that are part of the study objectives or endpoints

Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from medical records or other applicable source records, and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

SAEs, AEs, SSRs and PQIs in the medical records/other applicable source data that are not part of the study objectives and endpoints

Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from medical records/ source records.

8 Data Quality Control and Assurance

8.1 Quality Control

ICON will assure database quality by reviewing the data for missing values and accuracy. All data will be anonymized and kept confidential.

ICON maintains a high quality of work through a stringent quality control process that includes full internal quality control checks and will include:

- Review of study procedures and all methods detailed in the protocol.
- Confirmation that the source of the data and/or results has been documented and that results and data have been verified against the source.
- Checking the internal consistency of any research data presented in the document.
- Confirmation that the conclusions are accurate, objective, balanced, and consistent with other published or released results.
- Confirmation that the format and content of the document are aligned with applicable Shire requirements.
- Final annotated version of any disclosures (abstracts, posters and manuscripts).

8.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRBs/IECs may in rare cases wish to inspect the study. Upon receiving notification of such inspection, ICON must immediately contact Global Research and must make the records available as requested. The Inspector must be reminded up front that consent electronic consent has been obtained from the participants in this study.

8.4 Data Management

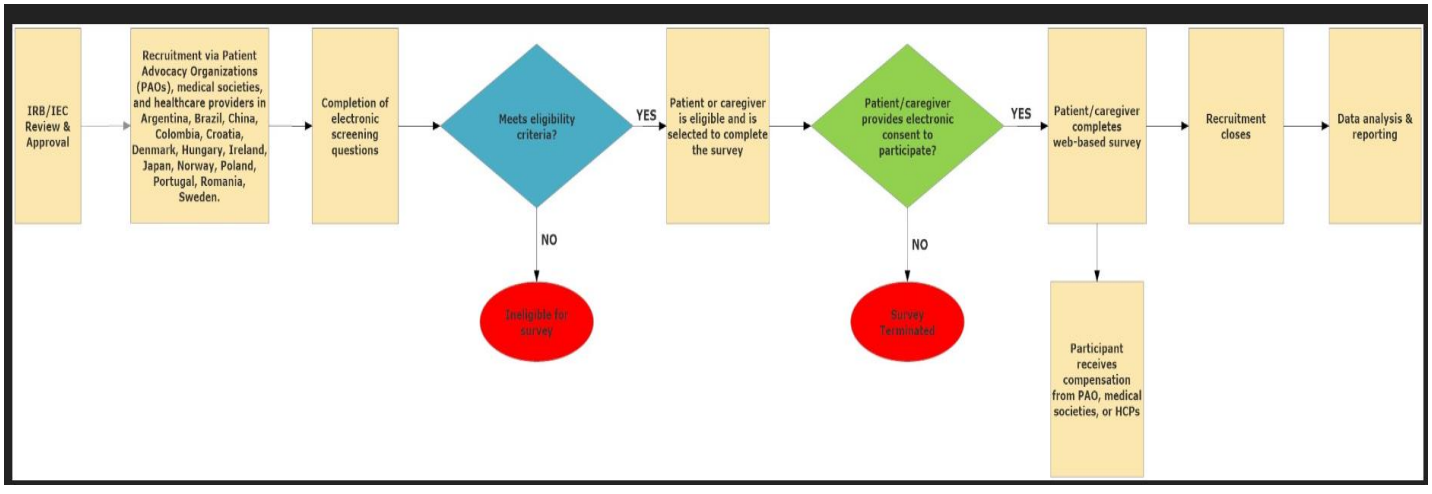
The survey will be hosted on secure SSL servers. Data files will be password protected and transferred using an encrypted system. ICON will maintain study records for 20 years per Takeda's master service agreement, or longer as required by local laws or regulations for participating country sites, following conclusion of the study and will notify the sponsor prior to the destruction of study records. ICON will give Takeda (or designee) access to all relevant source documents to confirm their consistency. Informed consent will be electronic and included in the survey database. In all cases, patient identifiers will not be collected or transmitted to the study sponsor.

8.4.1 Data Collection Tools and Flow

The Study Site will receive data collection tools access to electronic data capture etc.) from ICON.

Figure 1 provides a diagrammatic representation of the study design and data collection flow.

Figure 1



9 Statistical Methods and Determination of Sample Size

This section describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Study Report.

9.1 Statistical Analysis Plan

9.1.1 HAE Patient Survey

For each of the primary objectives of the HAE Patient Survey, data will be analyzed based on the total sample and each subgroup:

- Country
- HAE Type (Type I, II, normal functioning C1-INH, and unknown)
- By long-term prophylactic treatment status (LTP) (Currently on a long-term prophylactic treatment vs. not currently on a long-term prophylactic treatment)
    - Among those on LTP, comparison by number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
    - Among those on LTP, comparison of C1-INH, Androgens, and Tranexamic Acid
    - Among those on C1-INH LTP, comparison by number of attacks in the past 6 months
    - Among those on Androgen LTP, comparison by number of attacks in the past 6 months
- On-Demand Treatment Status (Currently using on-demand treatment vs. no on-demand treatment)
    - Among those on on-demand treatment, comparison by number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
- HADS subscale scores for anxiety and depression (for each subscale, including normal, mild, moderate, and severe)
- AECT Control Category (Controlled vs. Uncontrolled)

Objective 1: To describe patient characteristics, including demographics and clinical characteristics overall and separately for each subgroup.

- Appropriate descriptive summary statistics (e.g. mean and SD, median and interquartile range) will be presented for patient characteristics overall and for each subgroup. Demographic characteristics will include age, sex, education level, marital status, insurance type, residence, and employment status. Clinical characteristics will include HAE type, age at onset and diagnosis, family history; frequency of attacks; and severity, duration, and location of the most recent angioedema attack.

Objective 2: To describe the patient perspective on the humanistic burden of HAE including: **a)** disease control (AECT), **b)** health-related quality of life scores (SF-12 and AE-QoL), and **c)** psychosocial well-being scores (HADS) overall and for each subgroup listed below.

- Appropriate descriptive statistics will be used to summarize PRO scores on measures associated with patients' perspectives on the humanistic burden of HAE. The data will be presented overall and within each subgroup as relevant. For health-related quality of life, SF-12 domain and component scores as well as AE-QoL dimension and total scores will be described. HADS subscale scores will be summarized as indicators of psychosocial well-being.

Objective 3: To describe the economic burden associated with HAE as experienced by patients including the direct costs of illness, work productivity and absenteeism (WPAI-GH), treatment history, and health-care resource utilization overall and for each subgroup.

- Appropriate descriptive statistics will be presented for survey items and PRO scores related to costs of illness, impacts on work, history of treatment, and health-care resource utilization. The data will be provided overall as well as within each subgroup.

9.1.2 Caregiver of a Pediatric Patient Survey

For each of the primary objectives of the Caregiver of a Pediatric Patient Survey, data will be analyzed based on the total sample and each subgroup:

- Country
- HAE Type
- Age (categorical: <12 years, and 12-17 years)

- Number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
- On-Demand Treatment Status (Currently using on-demand treatment vs. no on-demand treatment)
- Prophylactic treatment status [Currently on a long-term prophylactic treatment (in total and broken out by prophylactic type) vs. not currently on a long-term prophylactic treatment]

Objective 1: To describe pediatric HAE patient characteristics, including demographics and clinical characteristics overall and separately for each subgroup.

- Appropriate descriptive summary statistics (e.g. mean and SD, median and interquartile range) will be presented for patient characteristics overall and for each subgroup. Demographic characteristics will include age and sex. Clinical characteristics will include HAE type, age at onset and diagnosis, doctors seen for diagnosis; time, duration, and location of the most recent angioedema attack.

Objective 2: To describe the caregiver perspective on the humanistic burden of HAE on both pediatric patients and caregivers overall and for each subgroup.

- Appropriate descriptive statistics will be presented for survey items related to patient and caregiver impacts. The data will be presented overall and within each subgroup as relevant.

Objective 3: To describe the economic burden associated with HAE as experienced by caregivers of pediatric patients including the direct costs of illness and work absenteeism overall and for each subgroup.

- Appropriate descriptive statistics will be presented for survey items related to costs of illness and impacts on work. The data will be provided overall as well as within each subgroup.

9.1.3 Caregiver of an Adult Patient Survey

For each of the primary objectives of the Caregiver of an Adult Patient Survey, data will be analyzed based on the total sample and each subgroup:

- Country
- HAE Type
- Number of angioedema attacks in the past 6 months (0 attacks, 1-3 attacks, 4-6 attacks, 7-12 attacks, ≥13 attacks)
- On-Demand Treatment Status (Currently using on-demand treatment vs. no on-demand treatment)
- Prophylactic treatment status [Currently on a long-term prophylactic treatment (in total and broken out by prophylactic type) vs. not currently on a long-term prophylactic treatment]

Objective 1: To describe the humanistic burden of caregiving for an adult HAE patient overall and for each subgroup.

- Appropriate descriptive statistics will be presented for survey items related to caregiver impacts. The data will be presented overall and within each subgroup as relevant.

Objective 2: To describe the economic burden associated with HAE as experienced by caregivers of adult patients including the direct costs of illness and work productivity and absenteeism overall and for each subgroup.

- Appropriate descriptive statistics will be presented for survey items related to costs of illness and impacts on work. The data will be provided overall as well as within each subgroup.

9.1.4 Analysis Plan for Secondary Objective(s)

Secondary Objective 1: To assess the relationship between HAE control and number of attacks, on HRQoL and emotional well-being among adult HAE patients.

- Regression models will be used to assess the relationship between AECT scores and number of HAE attacks on HRQoL (AE-QoL scores and SF-12 component summary scores) and emotional well-being (HADS emotional distress subscale score). The dependent variables will be AE-QoL scores and SF-12 component summary scores (in separate models) and the independent variables will be AECT scores or number of attacks. The model will also include covariates to control for background characteristics as appropriate.

Secondary Objective 2: To identify the demographic and clinical factors that impact quality of life and economic burden for patients with HAE among adult HAE patients.

- Multiple regression models using backwards stepwise selection and clinical relevance will be used to assess the demographic and clinical factors that are most important to PRO measure scores and the economic burden associated with HAE. The dependent variables, in separate models, will be the PRO measure scores (AE-QoL scores, SF-12 component summary scores and WPAI-GH scores) as well as direct cost of illness. The independent variables will include sex and clinical characteristics (including HAE type, long-term prophylaxis use, and long-term prophylaxis type) as appropriate.

9.1.5 Sensitivity Analyses

Not applicable.

9.2 Interim Analyses

No interim analyses are planned for this study.

9.3 Determination of Sample Size

For the main patient survey, a minimum sample size of 300 completed patient surveys is targeted. For each of the caregiver surveys (pediatric and adult), sample sizes of 250 and 200, respectively, are targeted.

In line with the objectives of the patient survey as well as recruitment feasibility assessments, the sample size of at least 300 participants may be considered sufficient to provide acceptable

levels of precision around the survey estimates (e.g. ±6% around a sample proportion of 0.50) and to allow sufficient power (80%) to detect differences between groups of equal size, which are at least moderate in magnitude (identified as an effect size of 0.50 or greater). In line with the objectives and recruitment feasibility of the caregiver surveys, sample sizes of at least 100 participants are sufficient.

It can be seen in Table 7, a sample size of 100 individuals would give at minimum (i.e., around a proportion of 0.50) a precision of ±0.098, with a resulting CI width of at most 0.20 (0.40 to 0.60 around an estimate of 0.50). If the sample size increased to 200 individuals the precision would increase to a minimum of ±0.069, with a resulting CI width of at most 0.14 (0.43 to 0.57 around an estimate of 0.50). Importantly, the increasing precision around samples of increasing size has the greatest impact up to a sample size of 400; sample sizes of 500 and 600 provide additional precision for the additional sample size, with the precision increasing only from 0.049 to 0.043 with an increase from 400 to 500, and from 0.043 to 0.039 from 500 to 600.

Table 7: Sample Size Calculations (Whole sample)

Sample size:	100	200	300	400	500	600
	Estimated proportion = 0.50					
Precision±	.098	.069	.056	.049	.043	.039
95% CI	.40-.60	.43-.57	.44-.56	.45-.55	.45-.54	.46-.54
Width of 95% CI	.196	.138	.112	.098	.086	.078
	Estimated proportion = 0.25					
Precision±	.085	.069	.049	.042	.038	.034
95% CI	.17-.34	.18-.32	.20-.30	.21-.29	.21-.29	.22-.29
Width of 95% CI	.170	.138	.098	.084	.076	.068

In terms of the precision of smaller groups of patients, such as those by country, the implications for varying sample sizes in terms of estimates of proportion are shown in Table 8.

Table 8. Sample Size Calculations (By country)

Sample size:	10	20	30	40	50	60	70	80	90	100
					Estimated proportion = 0.50					
Precision±	.31	.22	.18	.155	.139	.127	.117	.110	.103	.098
95% CI	.19-.81	.28-.72	.32-.68	.35-.66	.36-.64	.37-.63	.38-.62	.39-.61	.40-.60	.40-.60
Width of 95%	.62	.44	.36	.31	.278	.254	.235	.22	.207	.196
					Estimated proportion = 0.25					
Precision±	.270	.190	.155	.135	.121	.110	.102	.095	.089	.085
95% CI	-.02-.52	.06-.44	.10-.41	.12-.39	.13-.37	.14-.36	.15-.35	.16-.35	.16-.34	.17-.34
Width of 95%	.54	.38	.31	.27	.242	.22	.204	.19	.179	.170

These values indicate that for a sample with 20 participants, the precision around a sample estimate of 50% would be ±22%, meaning that (with 95% confidence) the true value in the population could lie anywhere from 28% to 72%. It thus would be difficult to draw meaningful conclusions from data obtained from such a small sample. The precision increases with the increasing number of participants, with the precision being ±10% for a sample size of 70 and a sample estimate of 25%, meaning that the true value could lie anywhere from 15% to 35% (i.e., overall width of CI=20%). This level of precision is still fairly low and will be unlikely to provide much scope, unless the effect size is large, for claiming any statistically significant group level differences.

9.4 Bias and Confounding

Selection bias may exist due to the route of recruitment via medical societies and patient associations. The survey will also rely on self-reported, retrospective data, which has the potential for recall bias [Bygum, et al., 2012].

9.5 Missing Data

No missing data are expected from the online survey data source up until the point when the participant either completes the survey or stops completing it before the survey end. The

questionnaires will be scored according to the developers' guidelines; and missing data will be handled accordingly. The frequency of any such missing data will be presented. No imputation of any missing data will be undertaken.

9.6 Significance Levels and Multiplicity

This is an observational survey study and findings are descriptive in nature. The study does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Participants will complete one-time, web-based survey. An internet protocol (IP) blocker will be incorporated in the survey in order to avoid multiple responses from the same participant.

10 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Takeda. The Final Study Report should be available within one year from collection of the last data point.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor may have the results of this study published.

The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

12 Archiving of Study Documentation

During the course of the study, ICON must as a minimum file the below essential documents in the Study File:

- Written agreement between the Sponsor and ICON.
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any, with the original signatures
- Informed consent forms in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required)
- Written IEC / IRB approval / vote according to local regulations

In all scenarios, ICON will maintain source documents for each participant in the study, consisting of the screening questionnaire for 5 years. ICON will give Takeda (or designee) access to all relevant source documents to confirm their consistency.

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14 Appendices

Appendix A: Recruitment Messages

Appendix B: Informed Consent Form

Appendix C: HAE Patient Survey

Appendix D: Caregiver of Pediatric Patient Survey

Appendix E: Caregiver of an Adult Patient Survey